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THE CLINICAL USE OF DEXTRAN AS A PLASMA SUBSTITUTE.

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WITH the developments in the use of intravenous therapy in the treatment of traumatic shock over the past fifty years, there has arisen a search for a satisfactory substitute for plasma—some substance which would be effective in restoring blood volume in shock, and at the same time not be toxic.

The search began in 1919, when Bayliss used solutions of gelatine, starch and dextrin to restore circulation after traumatic shock. Since that time several different types of preparations have been suggested, and recently polyvinyl pyrrolidone and dextran have been suggested as plasma or serum substitutes. Polyvinyl pyrrolidone had an extensive trial by the Germans during the recent war. It is now marketed as "Periston" and as "Plasmosan".

Dextran was first suggested as a plasma substitute by Swedish workers. In its crude form it is a bacterial polysaccharide prepared from cultures of *Leuconostoc mesenteroides*. As a by-product in the sugar-refining industry it has been known for years; but it was not until 1944 that Grönwall and Ingelmann (1944) suggested its use as a plasma substitute. Since that time extensive experimental and clinical studies have been made in Sweden (Bohmansson *et alii*, 1946). In England, Bull, Ricketts, Square and their colleagues (1949) have also studied its use as a plasma substitute. They found that it was efficacious in cases of burns, and that a sustained increase in venous return occurred in patients with surgical shock or hæmorrhage.

Dextran has also been investigated in America. Turner, Butler, Smith and Scudder (1949) gave dextran to a series of thirty volunteers. In ten of these cases reactions were observed. These reactions varied from pruritus to an attack of asthma. However, extensive use in the Mayo Clinic in some thousands of surgical cases has not led to any report of allergic reaction (Lundy *et alii*, 1950). With regard to the reactions reported by Turner and his colleagues, it is considered that the cause was protein impurity in an improperly prepared sample.

The Properties of Dextran.

Crude dextran as isolated from the cultures of Leuconostoc has a molecular weight of about 4,000,000. Particles of this size introduced intravenously are toxic, and lead to glomerular and capillary damage. Dextran for infusion purposes is a degraded product formed from crude dextran by acid hydrolysis. The aim of the process is to produce particles of molecular weight of 70,000 to compare as closely as possible with particles of serum albumin (molecular weight 68,000). The general range is 70,000 to 100,000, depending on how far the hydrolysis is carried. Complete hydrolysis of dextran leads to glucose. The physiological property of dextran making possible its use as a plasma substitute is that in 6% solution in saline it exerts a colloid osmotic pressure similar to that of plasma. As its actual osmotic pressure depends, not on the size of the particles, but on the number present, it is apparent that if the particles are near the minimum size to be retained in the blood vessels, then the osmotic pressure will be a maximum for the same concentration. When the particles are large the number of particles is less, and hence efficacy as a plasma substitute is correspondingly reduced. It appears that the optimum minimum size is a molecular weight of 68,000 to 70,000.

Ricketts, Lorenz and Maycock (1950) found that the amount of dextran appearing in the urine depended on

the intrinsic viscosity of the preparation. When the intrinsic viscosity—a function of molecular size—was increased, then the amount of dextran excreted in the urine was correspondingly reduced.

The dextran molecule, whilst synthesized from sucrose by the Leuconostoc organisms, contains no fructose, but is solely a glucose polymer. The polymer is formed by *d*-glucose units, built up by 1-6 glucoside linkages. The shape of the particle and also its foreign nature give rise to certain effects on the blood corpuscles—increased erythrocyte sedimentation and also pseudo-agglutination.

Scope of Present Study.

The reports of the Swedish, English and American investigators seemed to show that dextran was efficient in relieving shock. Cases of burns, post-operative shock and trauma have been studied. The present study was designed to investigate the use of dextran in cases in which serum would otherwise be given. For this purpose, only certain cases of shock are suitable. Burn shock is the best example of shock due to plasma loss, and in addition cases of post-operative shock and severe shock associated with dehydration were studied.

Cases of the following groups were investigated: (i) a preliminary group; (ii) burns; (iii) shock associated with severe dehydration; (iv) surgical shock.

In the three last groups blood samples were taken frequently for hæmatocrit, plasma protein, and plasma dextran estimations. The clinical state was observed closely. Blood pressure, pulse rate and changes in peripheral circulation were all watched carefully. In three cases urinary dextran estimations were carried out for periods varying from three to six days.

After the shock had been relieved, liver function and urea clearance and urea concentration tests were performed in six cases. In three cases, estimations of serum albumin and serum globulin contents were performed.

Altogether, 15 cases were studied. There were three control cases of burns.

Samples of dextran were generously provided by the Crookes Laboratories, Limited ("Intradex"), and Bengers Laboratories, Limited ("Dextran-Benger").

Clinical Reports.

Group I.

To gain experience with the handling of dextran, two preliminary infusions were performed. No reaction attributable to dextran or the infusion occurred in either case. The material was tolerated without rise in temperature or obvious change in pulse rate.

Group II.

The second group consisted of cases of shock due to burns. Three patients suffering from burns received dextran infusions. One was a man who had received electric flash burns to his whole body surface from a 33,000 volt discharge. He sustained a head injury as well, from which he died sixteen hours after his admission to hospital.

The case of a man who had 40% to 45% of his body surface burned is as follows.

W.B., a man, aged twenty years, was trapped in a fiercely burning grass fire. In trying to escape he fell forward into the fire. When admitted to the hospital four hours later, he was conscious and able to relate what had happened. His face, his neck, and the anterior parts of the trunk, and both forearms and hands, had severe second and third degree burns. There were large burnt patches of the same degree over the shoulders, back, buttocks, thighs and legs. It was estimated that between 40% and 45% of the body surface was affected.

Owing to the extent of his burns, no blood pressure or pulse readings were possible. It was not possible to take any blood initially for a hæmatocrit estimation. A cannula was inserted into a leg vein, and he was rapidly given several pints of dextran solution. The period during which the infusion was given, the progressive amounts received and the changes in hæmatocrit reading are shown graphically in Figure I. At one stage, after the hæmatocrit reading had begun to fall, it rose again. The rate of infusion was increased and the hæmatocrit reading fell again. A total of twelve pints (6·72 litres) of dextran solution was given in twenty-seven hours. This was followed by saline, sodium lactate and dextrose solution.

Eighteen hours after his admission to hospital the patient secreted 18 ounces of urine of specific gravity 1065. This was followed four and a half and six hours later by volumes of 20 and 30 ounces of urine with a specific gravity of 1030.

For the first three days the patient's condition was extremely grave. He had persistent high fever, his temperature being 102° to 103° F. He was irrational and able to take only small amounts of fluid by mouth. With his fever, his plasma showed evidence of jaundice, and he excreted porphyrins in his urine. However, on the fifth day his condition was a little better, and his burns were cleaned and dressed, for until this time the burned areas had been merely covered with dry dressings. After this he had a period of hyperpyrexia, but his condition was much improved next day. The remainder of his convalescence was extremely prolonged, but apart from very severe scarring he made a good recovery.

On this patient's admission to hospital, because of the extent of his burns, clinical examination was almost impossible. The hæmatocrit estimation was the only guide to his condition; but hæmoconcentration showed an adequate response to dextran therapy. The fact that urine was

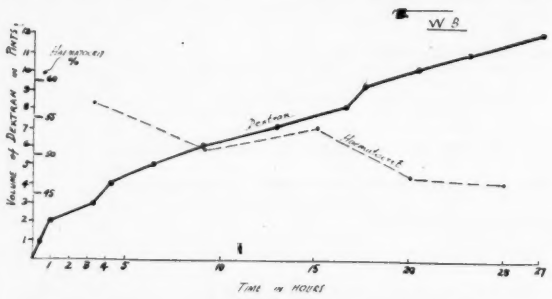

FIGURE I.

Dextran in the treatment of burn shock (patient W.B.).

secreted after eighteen hours suggested that shock was being relieved at that stage. However, the infusion was continued because of the amount of fluid loss that was continuing from the burned area.

A third patient suffering from burns, W.F., was treated with dextran. His burns covered about 30% of his body surface. He was admitted to hospital within half an hour of the accident. Shock was prevented adequately by the infusion of dextran. Details of the estimations performed in this case are described later.

Group III.

Six patients suffering from shock associated with severe dehydration were treated with dextran. These patients, varying in age from thirty to fifty-six years, were in a severely shocked condition owing to fluid loss or to an abdominal catastrophe. The conditions are classified as follows: E.W., intestinal obstruction due to strangulated ventral hernia; L.R., intestinal obstruction due to peritoneal band; C.B., severe diarrhœa; W.C., mesenteric thrombosis; S.B., severe shock associated with acute cholecystitis; M.C., ruptured duodenal ulcer. The first four of these patients were severely shocked. One of these cases is as follows.

L.R., a married woman, aged thirty-five years, was admitted to hospital with a history of severe right-sided abdominal pain and persistent vomiting of forty-eight hours' duration. There was a history of an abdominal operation nine years before. Examination revealed the patient to be a young woman, small, cyanosed and in obvious pain. The skin was loose and there was evidence of considerable loss of fluid from the subcutaneous tissues. The mouth and tongue were dry. The temperature was 97·2° F. The pulse

rate was 140 per minute, and the pulse had a very poor pressure and volume. The blood pressure could not be estimated. Examination of the abdomen revealed generalized rigidity with pronounced tenderness in both iliac fossæ. The urine had a specific gravity of 1018, was acid, and contained a trace of acetone and albumin.

A blood examination on a specimen taken at this time gave the following information: the hæmatocrit reading was 71% (normal, 42% to 47%); the plasma protein content was 8·6 grammes per 100 millilitres (normal, 6·0 to 8·0 grammes per 100 millilitres); the serum sodium content was 124 milliequivalents per litre (normal, 135 to 150 milliequivalents per litre); the serum potassium content was 4·1 milliequivalents per litre (normal, 4·0 to 6·5 milliequivalents per litre); the serum chloride content was 93 milliequivalents per litre (normal, 95 to 105 milliequivalents per litre).

On the assumption that saline was the nearest fluid to that which had been lost, this was given immediately by vein as normal saline. In two hours nearly two litres had been given, but the hæmatocrit reading had fallen to only 65%. The temperature had risen to 99° F. The pulse had improved in volume, but the rate was 150 per minute and the blood pressure could still not be estimated. After a further hour the blood pressure was 60 millimetres of mercury, systolic, and 40 millimetres, diastolic. After

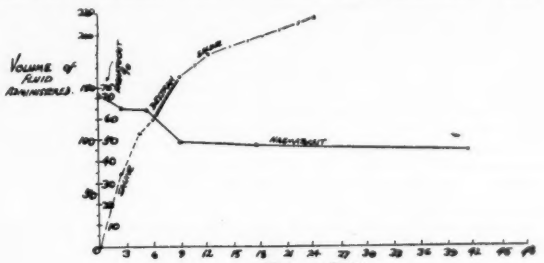

FIGURE II.

The effect of saline and dextran therapy in severe shock from intestinal obstruction (patient L.R.).

further waiting, and as no improvement seemed to be occurring, abdominal section was performed and a band strangulating the terminal portion of the ileum was divided. After operation the blood pressure was 90 millimetres of mercury, systolic, and 60 millimetres, diastolic, and the patient's condition was still poor. After seven hours of intravenous therapy, during which 3·3 litres of normal saline had been administered, the hæmatocrit reading had fallen only from 71% to 64%. No urine had been secreted. A review of the situation in this way demonstrated forcibly that normal saline had not been very effective in restoring plasma volume. Then 1·2 litres of dextran solution were given with a dramatic response; after two hours the pulse rate began to fall and the blood pressure began to rise. The hæmatocrit reading was 49% and the blood pressure was 110 millimetres of mercury, systolic, and 70 millimetres, diastolic. When the infusion of dextran was completed and after a further half-litre of saline had been given, the blood pressure was 130 millimetres of mercury, systolic, and 80 millimetres, diastolic.

Twelve hours after operation the patient had passed urine, her pulse rate was 120 per minute, her blood pressure was 130 millimetres of mercury, systolic, and 80 millimetres, diastolic, and the hæmatocrit reading was 47%. This progress is demonstrated graphically in Figure II.

Group IV.

Four patients suffering from post-operative shock received dextran. These patients had all undergone major abdominal operations, and in the first twenty-four hours after operation they were found to be sweating profusely, and of poor colour. The pulse was poor in volume and rapid—120 to 140 per minute. The blood pressure was reduced below the pre-operative level. Amounts of dextran solution from two to four pints were given to these patients.

One case is as follows.

E.B., a man, aged sixty-eight years, underwent total gastrectomy for carcinoma of the stomach. His condition was satisfactory until thirty hours after operation, when he complained of pain in the scrotum and right groin. A left inguinal hernia, which previously had been easily reducible, was now irreducible. On the right side a small femoral hernia which had previously been irreducible had become extremely tender. The diagnosis of strangulated femoral hernia was made, and the condition was relieved by operation under local anæsthesia. However, at operation a considerable amount of straw-coloured fluid escaped from the abdominal cavity, and it was thought that a leak had occurred at the site of anastomosis.

Twenty-four hours after this second operation it was found that the patient was cold and clammy. His skin was loose and could be gathered into folds. The pulse rate was 110 (previously between 60 and 80) per minute and the pulse was of poor volume. The blood pressure was 100 millimetres of mercury, systolic, and 80 millimetres, diastolic; previously it had been 130 millimetres of mercury, systolic, and 80 millimetres, diastolic.

The diagnosis of post-operative shock was made, and this was confirmed by a hæmatocrit reading of 57% (normal, 42% to 47%).

Since the first operation the patient had received two pints of blood and one litre of normal saline, and then a continuous infusion of dextrose (4%) in N/5 saline—three litres per day. He was given two pints of dextran solution over a period of three hours. At the end of the three hours the blood pressure was 120 millimetres of mercury, systolic, and 80 millimetres, diastolic, and the pulse rate was 100 per minute, but the pulse was of much better volume. The sweating had stopped, and the skin was warm. The hæmatocrit reading was 45%. Four hours after the infusion was begun the patient passed 12 ounces of urine, this being the first urine passed for twelve hours. His condition continued to improve. Twenty hours after the infusion was begun the blood pressure was 130 millimetres of mercury, systolic, and 80 millimetres, diastolic, the pulse rate was 90 per minute, and the hæmatocrit reading was 39%.

Convalescence was complicated by the development of a fistula in the lateral portion of the main abdominal wound, and by the occurrence of auricular fibrillation. Both these conditions were relieved, and after a prolonged convalescence the patient was discharged from hospital. Dextran proved efficient in relieving the shock which this patient developed after his second operation. Further, the improvement persisted after the infusion was stopped.

The Effects of Dextran Infusion.

Blood Changes.

The estimation of the amount of dextran in the serum, carried out by the method of Hint and Thorsen, showed that concentrations varying from 1·5 to 2·0 grammes per 100 millilitres could be built up rapidly in twelve hours. In one case a level of 1·70% was reached in four and a half hours. After infusion dextran remained in the circulation in detectable amounts until the sixth to eighth day. The duration depended on the amount administered, but as a minimum, after two pints of dextran solution, some could be detected until the sixth day.

In their series, Bull, Ricketts, Squire and their colleagues (1949) estimated plasma protein and plasma dextran contents in serial samples of plasma. This was also done in the present series of studies. The finding of Bull *et alii*, that the sum of plasma dextran and plasma protein tended to remain constant, was confirmed in that the sum of serum dextran and serum protein was found to remain approximately constant. Figure III demonstrates this relationship.

In the same three cases, albumin and globulin estimations were performed on serial samples of serum taken after dextran infusion. The serum albumin content was found to remain approximately constant, whilst the serum globulin content fell immediately after the infusion.

With the hæmoconcentration and reduced plasma volume characteristic of shock, both serum albumin and serum globulin concentrations are raised initially. The most convenient way of demonstrating any alteration in proportions of serum albumin and serum globulin contents is by using the albumin-globulin ratio. When the serum albumin content remains approximately constant and the serum globulin content falls, the change is demonstrated by a rise in the ratio. The use of the ratio in this way enables one to see the changes independently of the initial

concentration of plasma protein. Figure III shows the change in albumin-globulin ratio, the total serum protein content and the serum dextran content which followed the infusion of dextran in a case of burns. It can be seen from the figure that in this case the curves for albumin-globulin ratio and serum protein content are almost mirror images of each other, and the curve for albumin-globulin ratio closely follows the curve for serum dextran content.

These findings suggest that it is the serum globulin content which is affected by dextran infusion. This change was followed in two other cases in which dextran infusion had been given for post-operative shock and shock associated with dehydration respectively. This would suggest that the relationship is not specific for burns, but results from the administration of dextran.

Renal Function.

In a small series of cases the urinary excretion of dextran was estimated. It was found that between 10% and 13% of the dextran infused was excreted in the urine in the first seventy-two hours.

Patient W.B., whose case was described earlier, excreted urine with a specific gravity of 1065. This urine was extremely viscous, as might be suspected. This was the highest specific gravity of urine in any case studied. Generally the specific gravity was 1025 or higher in the early specimen, and fell to 1015 or 1010 within twenty-four hours.

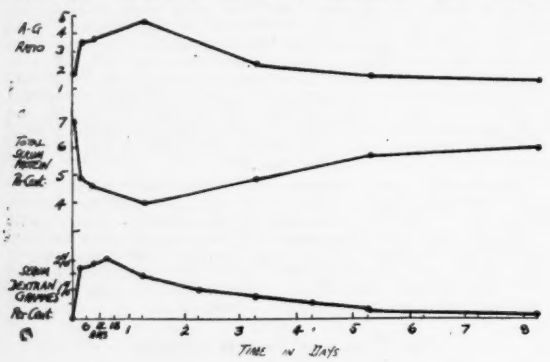

FIGURE III.

Changes in serum protein and albumin-globulin ratio following dextran infusion.

With two exceptions renal function was adequate after dextran infusion. When possible all patients had combined Fowweather and Van Slyke clearance tests performed. Preinfusion data are not available, so that it is extremely difficult to gauge the effect of the infusion on renal function. Table I shows the results in three uncomplicated cases of shock. The urea clearance test gives some indication of renal function under urea load.

Two patients with very severe shock developed anuria or severe oliguria after the shock had been relieved. In both these cases there was a period of prolonged and severe hypotension. Both patients were middle-aged, so that the effect of such hypotension was probably enough to produce renal damage. Other patients, who were younger and as severely, if not more severely, shocked received larger amounts of dextran without ill-effect.

Liver Function.

Clinically, dextran appeared to have little effect on the liver. One patient with severe burns became jaundiced and excreted porphyrins in the urine; but as no other patients did this, it seems likely that this was due to the severe toxic reaction resulting from such severe burns.

Liver function tests were performed at varying periods after dextran infusion. Again no preinfusion data were available. A series of results is shown in Table II.

It can be seen from these results that no constant picture follows dextran infusion. In three cases the serum alkaline phosphatase level was raised, but in only one case, that of W.B., who had toxæmia associated with severe burns, was the level abnormally high. In the case of A.C., the cephalin-cholesterol flocculation test gave a very strongly positive result; but this is the only case in which a significant change occurred after a lapse of time. The patient E.W. gave positive responses to flocculation tests, but in her case there was a possibility of preexisting liver damage associated with the use of a hair dye.

TABLE I.

Urea Clearance after Dextran.

Patient.	Diagnosis.	Time of Test After Infusion.	Urea Clearance (Van Slyke) Before Dextran Infusion.	Urea Clearance (Fowweather) After Dextran Infusion.
A.C.	Post-operative shock.	12 days.	77%	107%
L.R.	Dehydration.	10 days.	98%	71%
W.F.	Burns.	35 days.	79%	123%

The change in the flocculation test result is generally associated with an increase in the γ globulin fraction of the serum protein. The changes are too ill-defined to be of any significance. Either dextran has little effect on the liver, or else present means of detection of liver damage are relatively insensitive. The change in serum globulin content described earlier suggests that there must be some effect on the liver.

In one case a sample of bile was obtained in the first twenty-four hours after infusion. No dextran was detected in this sample.

TABLE II.

The Effect of Dextran on the Liver as Shown by Liver Function Tests.

Patient.	Time of Test After Infusion.	Icteric Index.[1]	Serum Alkaline Phosphatase Content (King-Armstrong Units).[2]	Serum Colloidal Gold Reaction.	Cephalin Cholesterol Flocculation.	
					Twenty-four Hours.	Forty-eight Hours.
				0 to 2		
A.C.	7 days.	8	20·6	2	+++	++++
	29 days.	4	22·2	3	–	Weak +
	61 days.	7	15·6	4	–	–
L.R.	3 days.	4	5·5	0	–	–
	10 days.	5	8·8	0	–	–
W.B.	20 days.	7	35·5	2	–	–
	139 days.	8	10·0	0	–	–
E.W.	5 days.	8	8·2	2	++	+++
	19 days.	13	9·4	2	++	+++
W.F.	5 days.	3	11·7	1	–	Weak +
E.B.	4 days.	8	17·2	0	–	–

[1] Normal, 4 to 6.

[2] Normal, 3 to 13 King-Armstrong units.

Pathological Changes.

Whilst a number of patients who received dextran died from their primary condition or the shock associated with it, only two subjects were examined *post mortem*.

S.B., a woman, aged sixty years, was an in-patient on account of an attack of acute cholecystitis. She had been known to be a diabetic for many years. At the time of her admission to hospital she had been jaundiced, but this condition had decreased. Her progress was satisfactory until the seventh day, when her temperature rose to 103° F. and her pulse rate rose to 130 per minute. She began to retch and vomit frequently. There was no complaint of pain. The pulse soon became impalpable. The blood pressure fell from a previous level of 150 millimetres of mercury, systolic, and 90 millimetres, diastolic, to 50 millimetres of mercury, systolic, and 30 millimetres, diastolic. The patient's colour was good. There was no sweating. The tongue was moist

and clean, the skin was dry and lax, the respirations numbered 32 per minute, and air hunger was present. In the abdomen there was no distension, and apart from some guarding near the right costal margin with a palpable mass, examination gave negative results. (These physical signs were virtually unchanged since the patient's admission to hospital.) The urine was free from sugar and ketone.

An intravenous infusion of dextran was begun. A hæmatocrit reading obtained from blood taken when infusion apparatus was being set up was 41%. Because the patient was so intensely shocked, and though no primary cause could be detected, it was decided to continue the infusion. Two hours later, after one and a half pints of dextran solution had been given, the pulse rate was 120 per minute and the blood pressure was 75 millimetres of mercury, systolic, and 45 millimetres, diastolic. After two pints of dextran solution had been given, the hæmatocrit reading was 33%. The pulse rate and blood pressure remained the same. The patient was then given one pint of blood. Her condition gradually deteriorated until she died seven hours after the incident of shock began.

At the post-mortem examination (nine hours after death) there was evidence of acute cholecystitis and chronic pancreatitis. There was some œdema of the lungs. Apart from atheromatous changes in the aortic cusps the heart was not grossly diseased. The left coronary vessels were slightly atheromatous. There was no obvious orifice for a right coronary artery. The left coronary artery ran a supraventricular course and branches ran downwards over both ventricles.

The kidneys were pale. Examination of sections showed that many of the convoluted tubules contained granular eosinophilic material, and that this was present lower in the nephrons to a lesser extent. In many places this material appeared to have been formed from the breaking-down of red cells, but it is not certain that hæmorrhage had occurred in the tubules. However, hæmorrhage had occurred into the interstitial tissues in places, sometimes around cortical tubular structures, sometimes in the medulla. The glomeruli appeared rather hypercellular, and occasionally Bowman's space contained fine eosinophilic particles. It would seem that, apart from post-mortem change, there was some tubular damage, mostly in the lower nephron.

The second case was that of a man, K.A., aged thirty-five years, who was working on a 33,000 volt transformer when an electric flash occurred. He received flash burns over almost the whole of his body surface, and fell nine feet to the ground from the effect of the discharge. He was admitted to hospital, and when examined one hour after the accident occurred he was conscious and complaining of cold. He had second and third degree burns over the whole of his body except for patches on his legs. His pulse was too rapid and too weak to count. No blood pressure measurements could be made because of the extent of the burns. Dextran infusion was begun. He was given two pints under pressure in a period of an hour. After this the pulse pressure improved a little, but the rate was still too rapid to be counted. Blood taken one and a half hours after the infusion began had a hæmatocrit reading of 51%, and this value was unchanged over the next six hours.

Three hours after his admission to hospital, the patient lapsed into unconsciousness. His right pupil dilated and became fixed, and similar changes occurred in the left pupil. An intracranial hæmorrhage (probably middle meningeal) was diagnosed, but the clinical condition did not warrant operation. The patient died seventeen hours after his admission to hospital. He received a total of twelve pints of dextran solution.

At the post-mortem examination there was an extradural and also an intracerebral hæmorrhage in the right of the temporal region. The skull was fractured in this region.

The kidneys were pale in the cortex and congested in the medulla. On section Bowman's capsule was seen to be expanded. The cells of the distal convoluted tubules were much damaged. These features were probably associated with the shock. In the upper nephron the tubular cells showed hydropic degeneration of the type commonly described as sucrose necrosis. This was probably due to the infusion and resulted from the hypertonicity of the dextran solution.

Discussion.

In considering the effectiveness of any plasma substitute, Bull and his colleagues (1949) set forth certain criteria for the qualities of such a substance. They are as follows: (i) Colloid solutes should be retained in the circulation until their place can be taken by natural proteins. (ii) Solutions used for infusion should have a viscosity and an osmotic pressure similar to those of plasma. (iii) Composition as manufactured from batch to batch should be constant within narrow and definable limits. (iv) The solution should preserve its qualities under varying conditions of storage. (v) It must not be toxic either locally or generally. (vi) It must not induce fever. (vii) It must not induce sensitization. (viii) It must not be stored for long periods in the tissues. (ix) It must not act as a diuretic.

Whilst fulfilling many of these requirements, dextran has certain definite disabilities. It appears that any technical difficulties in its manufacture and storage have been overcome and the solution does not deteriorate after storage. Further, it is manufactured free, or almost free, of all protein impurities.

In the cases studied in the present series no evidence of toxicity, no febrile reactions and no sensitization phenomena were observed.

Dextran remains in the circulation until the plasma proteins have returned to their former level. However, it has been shown that dextran has certain specific actions on the plasma proteins. Generally in shock the plasma proteins are somewhat concentrated, and after adequate therapy the concentration falls. Dextran infusion produces a further fall—probably an active depression or withdrawal of plasma protein occurs. The protein concentration falls as rapidly as the dextran concentration rises, suggesting that the protein is actively withdrawn from the circulation, to return as the serum dextran level falls.

Further, the experiments described earlier suggest that the globulin fraction may be withdrawn specifically, rather than that there is any general suppression of plasma protein formation. This withdrawal of globulin from the circulation may not be a good thing from the general point of view of the patient, but from the mechanical point of view, reduction of globulin will upset osmotic balance much less than if the albumin were withdrawn. Globulins are larger particles than albumin, and so weight for weight their osmotic activity is much lower. That no permanent damage results from the withdrawal of the globulins is suggested by their ready return as dextran disappears from the circulation. This depression of circulatory globulin may not be specific for dextran, but possibly follows serum infusion as well, and is probably only a factor in preventing the plasma from becoming grossly hypertonic in relation to the remainder of the extracellular fluid. This would suggest that the giving of serum in states other than hypoproteinæmia or shock may temporarily depress the liver in its function of protein synthesis.

The length of time for which dextran remains in the circulation seems to depend on particle size. Thus the smaller fractions pass through the glomerular filter into the tubules and are excreted in the urine. The capillaries of the glomerular tuft are similar to those elsewhere, so that the smaller dextran molecules will pass through into the interstitial fluid from the general capillary bed. If 13% of the dextran given is detected in the urine in the first seventy-two hours, a corresponding amount must also have passed into the interstitial fluid and be lost from the blood. These smaller dextran particles will have a greater osmotic activity, gramme for gramme, than the larger ones, and so if the samples of dextran infused contain a large number of the smaller particles, the effectiveness of the dextran in restoring colloid osmotic pressure will be impaired, not only from the effect of its loss to the circulating blood, but also because of the effect in opposing the osmotic activity of the plasma protein and plasma dextran particles within the blood vessels.

Thus it can be seen that under certain circumstances dextran can act as an osmotic diuretic, for the material passing into the tubules will enforce water loss to enable excretion to be carried out efficiently. The degree to which the osmotic diuresis is permitted to withdraw water from

the body will depend to a large extent on the individual case. Thus in the case of W.B. the first sample of urine was of specific gravity 1065. This must represent extreme concentration and water conservation. The fact that there were 18 ounces of this specimen would raise the question of what would be the effect if the kidney had not conserved water. The next samples were of specific gravity 1030. A possible advantage of this diuretic activity may be that the kidney is forced to secrete urine. However, there seems little value in this, as surely the kidney will secrete urine when shock is relieved and normal relationships are reestablished.

The experiments of Terry, Hawkins, Church and Whipple (1947) on hyperproteinæmia in dogs are of interest in comparison with the renal excretion of dextran. Injection of plasma into dogs raised the plasma protein level. When the level reached a value somewhere between 9·6 and 10·4 grammes per 100 millilitres, proteinuria appeared. An interval of four to twenty-six days occurred between the injection of plasma and the development of proteinuria. Larger amounts of protein decreased the time interval. It was found that the albumin appeared in the urine in relatively greater amounts. These experiments suggest that there may be a renal threshold for protein. This would suggest that with dextran infusion a similar effect may occur if the kidney treats dextran molecules as albumin molecules, which they resemble in size but not in shape. If this is so, the dextran will be secreted in the urine in amounts depending on the total of plasma dextran *plus* plasma protein. The larger dextran particles may then appear in the urine if the rate of infusion is too rapid or if the removal of globulin from the circulation is impaired. In the animal experiments described by Terry, Hawkins, Church and Whipple, the proteinuria ceased when the infusion stopped. There were no demonstrable renal lesions. A mechanism of this type may prevent the development of hypertonic plasma, and may explain the transient albuminuria seen after shock when, with the reduction of plasma volume, the plasma proteins have been concentrated.

The possible effects of this concentrated osmotic activity on the kidney are difficult to assess. In the series there were two cases of lower nephron nephrosis. Both these patients were aged over forty-five years, and both must have had a period of hypotension and shock of at least twenty hours. From the clinical point of view it seems that there is ample cause, apart from the effect of dextran, to account for the renal damage. On the other hand, there are definite lesions to be detected in the kidneys of the two subjects who came to post-mortem examination. In neither of these cases was there anything to suggest preexisting renal disease; but the findings on section are those of lower nephron nephrosis in one and sucrose nephrosis in the other.

Did renal damage of this degree develop in all the other patients who received dextran? If this did happen, then the residual functional disturbance was slight with two exceptions. The fact that so few patients developed renal disturbance after dextran infusion suggests that dextran may not cause much renal damage. However, the changes described in sections are so pronounced that the possibility of their having been caused by dextran must be seriously considered. Goldenberg, Crane and Popper (1947), after experiments in dogs and rabbits, found renal tubular lesions typical of sucrose nephrosis, but there was no evidence of impaired function.

The fate of dextran after infusion remains obscure. It has not been adequately demonstrated that the body is able to hydrolyse dextran into its component glucose molecules. Engstrand and Aberg (1950) suggest that dextran which is not eliminated by the kidneys or taken up by the reticulo-endothelial system is excreted into the bowel. As the capillaries of the small intestine and the liver are known to be permeable to albumin, it is quite possible that dextran is eliminated in this way. None was detected in the bile in the one case in which this was examined after infusion. If large amounts of dextran are excreted into the lumen of the bowel, Engstrand and Aberg suggest that care should be exercised in its infusion in cases of intestinal obstruction. It remains to be demonstrated what happens to the remainder that is not excreted from the body.

The effect of dextran on the liver is also obscure, in that liver function tests failed to demonstrate any specific change. Examination of sections of the liver taken at post-mortem examination revealed no histological changes. It seems certain that no diffuse parenchymatous liver damage occurs as a result of dextran infusion.

The antigenic activity of dextran remains to be considered. In none of the cases in the present series was there any reaction to infusion. The effect of repeated infusion after a period of at least ten days remains to be described. Patients suffering from shock seldom require repeated administration of colloids to restore blood volume. With the use of salt-free dextran in the treatment of hypoproteinæmic œdema associated with sodium retention, there will be a greater chance of the development of reactions. Its freedom from naturally occurring antibodies gives dextran one advantage over serum. The local venous reaction to serum is well known and often causes considerable difficulty when it is desired to administer fluid quickly. No such effect has been observed with dextran, and it is possible to administer the fluid as quickly as the situation may require.

The case of L.R. illustrates several important features. A severe degree of shock was present on the patient's admission to hospital. Severe hæmoconcentration was present with concentration of the plasma protein, though not to the same degree, suggesting that there had been loss of protein from the plasma, accompanying the severe shock.

In spite of the concentration of the plasma, the serum sodium content was only 124 milliequivalents per litre. This would represent a concentration of 81 milliequivalents per litre if hæmoconcentration had not occurred (and calculated on a normal hæmatocrit reading of 45%).

The amount of sodium administered as normal saline before dextran was given was 515 milliequivalents. This should have led to a greater correction of the hæmoconcentration. The additional sodium from the dextran was only 187 milliequivalents, and it is not conceivable that this small addition should have led to such a change in hæmodynamics.

The presence of a concentration of plasma protein of 8·6 grammes per millilitre should be enough to hold a volume of fluid in the plasma at the expense of the extracellular space—but apparently this was not the case. There must have been some other disturbance of osmotic balance which the 1·2 litres of dextran solution were able to correct, so bringing the saline that had been administered earlier back from the interstitial fluid into the plasma.

Winkler, Danowski and Elkinton (1946), in their experiments on salt depletion in dogs, found that if colloid solutions were administered, a smaller volume of fluid was required than would have been the case if normal saline had been given to achieve the same degree of relief. These findings would suggest that in salt depletion other factors are active in disturbing osmotic balance, and that plasma protein, even though concentrated, is not so effective as it should be in maintaining equilibrium. It may be that the circulation is so disturbed under these conditions that the homœostatic mechanisms described earlier are upset. This would suggest that in the treatment of shock with dehydration, dextran has a place when hæmoconcentration is severe. No attempt has been made in this study to differentiate between the two types of dextran used.

Methods of Estimation.

The serum dextran content was estimated by the method of Hint and Thorsen (1947), and the urinary estimation was carried out by a modification of this technique. Serum protein, albumin and globulin contents were estimated by the method of Wolfron, Cohn, Calvary and Ichiba (1948).

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Summary.

Dextran was used in the treatment of patients suffering from shock due to burns, from shock associated with dehydration, and from shock occurring after operation. In all these cases it was effective in restoring blood volume and relieving hæmoconcentration. Blood pressure was improved, and the pulse rate fell.

In studying the after-effects of dextran infusion, it was found that the serum globulin level was depressed, and this returned to normal as the serum dextran level fell. There was no impaired renal function after infusion, except for two patients who developed lower nephron nephrosis. The pathological changes in the kidneys of two patients who died during the treatment of shock are described, and their relationship to the infusion of dextran is considered. No specific change in liver function tests was found after infusion.

The implications of these findings have been discussed in detail, and though there are certain problems with regard to the end results of dextran infusion that need elucidation, it would appear that this substance is an adequate substitute for plasma in the treatment of shock.

Acknowledgements.

I am indebted to the members of the Dextran Subcommittee and many other members of the honorary staff of the Royal Adelaide Hospital for their advice and cooperation. Without the ready assistance of the staff of the Resuscitation Clinic, much of this work would not have been possible. I am grateful to Dr. J. O. Poynton, Director of the Institute of Medical and Veterinary Science, for his advice and for the provision of facilities which made these studies possible. Mr. E. Wyld and Mr. J. Marshall gave me technical assistance. I am indebted to Mrs. P. Spencer, of the Clinical Biochemistry Division of the Institute, who performed the serum protein estimations. My thanks are due to Professor J. S. Robertson, Dr. R. Osmond and Dr. R. A. Barter for their advice and assistance.

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INTRAHEPATIC OBSTRUCTIVE JAUNDICE.

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THE differential diagnosis between jaundice due to extrahepatic biliary obstruction and that due to diffuse hepatocellular disease has in recent years been facilitated by the use of a combination of biochemical tests. Elevation of the serum alkaline phosphatase level in the absence of bone disease indicates obstruction to the excretion of bile and possibly change in the epithelium of the bile channels (Burke, 1950), whereas abnormal flocculation test results indicate changes in the serum proteins and protein-lipide complexes dependent upon abnormal function of liver cells. In cases of extrahepatic biliary obstruction, in addition to the clinical features, there is usually a rise in the serum alkaline phosphatase level associated with normal results to flocculation tests in the early stages. However, if obstruction persists for a sufficient length of time, liver cell function may suffer, so that the flocculation test results may become increasingly abnormal late in the clinical story. In primary hepatocellular disease, in most cases the flocculation test results are abnormal at the onset of the jaundice.

In acute infective hepatitis it is almost universal for the patients to notice early in the disease, in addition to darkening of the urine, a definite paleness of the stool; the latter may persist for a varying period, suggesting a diminution of bile entering the gut. Biochemically there is at this stage an increase in the serum bilirubin content, and the serum alkaline phosphatase level is usually moderately elevated. With recovery in most cases the serum bilirubin level falls first and the flocculation test results revert to normal later. The alkaline phosphatase reaction tends to parallel the serum bilirubin content in most cases. It has been postulated that jaundice in hepatitis is not due entirely to failure of the damaged liver cell mass to excrete adequately the normal blood load of bilirubin, but that there is in addition an obstructive factor in the small bile channels within the liver. Conclusive evidence is lacking and mechanisms are in dispute (Lichtman, 1949). Nevertheless the concept of intrahepatic obstructive jaundice is helpful to explain certain clinical features.

CASE I.—J.A., a female patient, aged twenty-five years, a *primipara*, was admitted to King George V Hospital on March 27, 1951. The date of the last menstrual period was August 18, 1950, and the estimated date of confinement was May 28, 1951. The patient told the story that she had been perfectly well until two weeks prior to her admission to hospital, when she had developed aches and pains in the limbs and back and some headache. There was no sore throat, nasal discharge or cough. These symptoms were associated with anorexia, nausea and some vomiting, mainly of solid foods, although fluids were well tolerated. This state of affairs lasted for one week, and although the vomiting ceased, anorexia persisted until her admission to hospital. During the second week the patient had diarrhœa, passing four or five loose stools per day. These were paler in colour than normal and associated with lower abdominal colicky pain prior to defæcation. Four days prior to her admission to hospital the patient noticed that her urine was very dark in colour, and two days prior to her admission she was noticed to exhibit generalized jaundice, which had gradually deepened in colour. On the night prior to her admission the diarrhœa had been more severe, and in the morning the patient had a painless loss of bright blood *per vaginam*. There had been no history of contact with other patients with jaundice or of injections in the previous six months, nor had the patient ever had a previous episode of jaundice. There had been no other symptoms.

On examination of the patient, jaundice was obvious; there was no fever. No enlarged lymph glands were palpable, nor could the spleen be felt. The liver was just palpable on deep inspiration, was smooth in outline and extremely tender to touch. Vaginal examination revealed no abnormality other than some bright blood on the examining finger. Fœtal heart sounds were present and the height of the fundus confirmed the duration of pregnancy. There was no other significant

abnormality on physical examination. The urine contained bilirubin according to the ward (iodine) test.

The clinical diagnosis of acute infective hepatitis was supported by the biochemical findings as follows: the serum bilirubin content was 12 milligrammes *per centum*, the thymol flocculation was "++++", the serum alkaline phosphatase level was 22·2 King-Armstrong units. A blood count gave the following information: the hæmoglobin value was 11·9 grammes *per centum*, the red cells numbered 3,980,000 per cubic millimetre; the total and differential leucocyte counts were normal; the prothrombin index was estimated at 34%. Vitamin *K* was given parenterally, the vaginal bleeding rapidly ceased and the prothrombin index estimated three days after her admission to hospital was 89%. The patient was kept at rest in bed with a full diet.

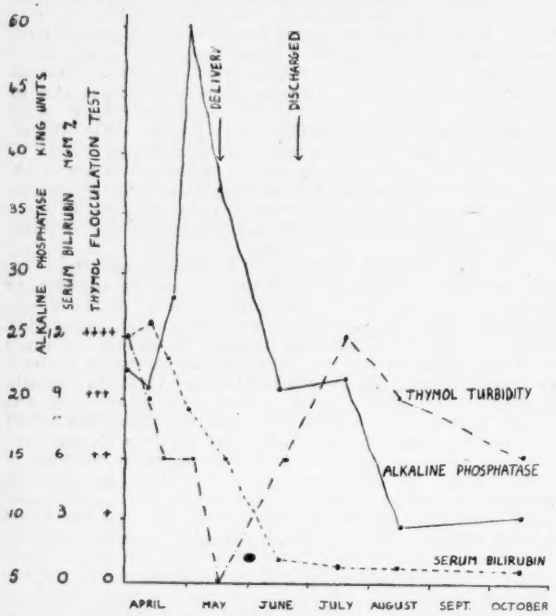

FIGURE I.

Diagram showing the results of serum bilirubin, thymol flocculation and serum alkaline phosphatase tests in a case of infective hepatitis with prolonged course and apparent obstructive features during recovery (Case I).

Complete cessation of diarrhœa occurred after her admission to hospital. She continued to show obvious jaundice and the stools continued to be pale although not completely acholic. In addition the patient complained of considerable pruritus. There was no abdominal pain or discomfort, although there was intermittent left sciatica. This state of affairs persisted without gross clinical change for six weeks, although hepatic tenderness and anorexia were absent after the first two weeks, and the patient felt comparatively well. The results of serial liver function tests are shown in Figure I. It was noted that the serum alkaline phosphatase level was increasing, although the thymol flocculation test result was becoming less strong, and in view of the persistent jaundice with severe pruritus and pale stools, the possibility of primary extrahepatic obstructive jaundice was considered, but rejected chiefly on the mode of onset of the illness and the absence of abdominal pain. A plain X-ray film of the abdomen revealed no opaque gall-stones. On May 15, 1951, the patient was delivered of a normal male child weighing five pounds eight ounces after a short labour and without excessive blood loss, and he was artificially fed. Pruritus and stool pallor receded, but the jaundice persisted, although gradually diminishing in intensity, until the first week in June, a total of two and a half months from its onset. The patient was discharged home on June 19, feeling well, and had a convalescence of two months with considerable restriction of activity. Follow-up examination has shown her to have remained perfectly well; there has been no jaundice, the liver is still palpable but not tender on deep inspiration, the spleen is not palpable, and although the serum Lange test result has returned to normal, the thymol flocculation test result is still abnormally high but decreasing. A cholecystogram on August 20 showed the gall-bladder to be normal according to Graham's test.

It will be seen that six weeks after the onset in this case of prolonged hepatitis with clinical recovery the picture was one of painless jaundice, pale stools, itching and considerable increase in serum alkaline phosphatase content with a normal thymol flocculation test result. A concept of intrahepatic biliary obstruction occurring during an episode of infective hepatitis, which may predominate during recovery, as in this case, seems to fit the clinical and biochemical findings. It is conceivable that if a patient was first investigated biochemically at this stage—to explain why jaundice was persisting longer than usual in infective hepatitis—an erroneous diagnosis of primary biliary obstruction might be made (Coleman, 1950; Steigmann, Meyer and Popper, 1949). This feature of apparent intrahepatic obstruction during an episode of diffuse hepatic disease with jaundice is not uncommon. Steigmann and Popper (1948, 1949) found this phenomenon in 66·6% of a series of cases of homologous serum jaundice, in 43·5% of cases of toxic cirrhosis, in 35·3% of cases of infective hepatitis and in 19·3% of cases of cirrhosis with jaundice.

Certain cases of jaundice of more prolonged duration with a predominantly obstructive picture, in which no extrahepatic lesion can be found, are more difficult to explain. Dible, McMichael and Sherlock (1947) presented five cases of prolonged jaundice of an obstructive type in elderly patients, in which no organic obstructive lesion could be found, and in which the histological findings in the liver were consistent with the diagnosis of obstruction. In these cases, however, the serum alkaline phosphatase level was normal. Watson and Hoffbauer (1946) described eight cases of prolonged jaundice following infective hepatitis, characterized by a partly obstructive picture with itching, pale stools, and increase in blood cholesterol and serum alkaline phosphatase contents, in which liver biopsy studies did not suggest intrahepatic biliary obstruction, and the authors suggested that the functional abnormality was increased permeability of the small cholangioles with regurgitation of bile; they called the condition "cholangiolitic hepatitis", which could either resolve very gradually or proceed to a biliary type of cirrhosis.

Biliary cirrhosis in the great majority of cases is secondary to ascending cholangitis, often intermittent, or to an extrahepatic obstructive lesion, although in certain parts of the world schistosomiasis and infestation with liver fluke appear to play a part. Nevertheless, cases of primary biliary cirrhosis in the absence of these factors are well recorded. Recently Ahrens, Kunkel *et alii* (1950), in reviewing the literature and presenting 17 new and well documented cases, have clarified the criteria for diagnosis and the course of the disease, although not expressing any opinion as to ætiology. The authors describe primary biliary cirrhosis as characterized by hepatomegaly, predominantly in middle-aged patients, associated with prolonged (two to eleven years) obstructive jaundice (as evidenced by itching, pale stools, increased serum alkaline phosphatase activity, low stool stercobilin content); they state that no extrahepatic obstructive lesion can be found at autopsy, there is no clinical or pathological evidence of cholangitis, and evidence of liver cell abnormality (flocculation tests) and liver failure in any form is late in appearance. Histological examination, both by liver biopsy and at autopsy, shows changes which can be differentiated in some cases from secondary biliary cirrhosis, chiefly in the absence of proliferation of bile ducts in the portal tracts and the absence of pronounced inflammatory cuffing around the large and small bile ducts. A characteristic abnormality is the progressive elevation of the serum lipid level, resulting later in skin and other xanthomatous formation, depending on the degree and duration of lipid elevation, so that prexanthomatous and xanthomatous stages of the disease are recognized. However, the authors emphasize that this feature of blood lipid elevation is not peculiar to primary biliary cirrhosis alone, and that elevated serum lipid levels and xanthomata do occur in prolonged obstructive jaundice of any cause; the reason why xanthomatous

ILLUSTRATIONS TO THE ARTICLE BY B. P. BILLINGTON

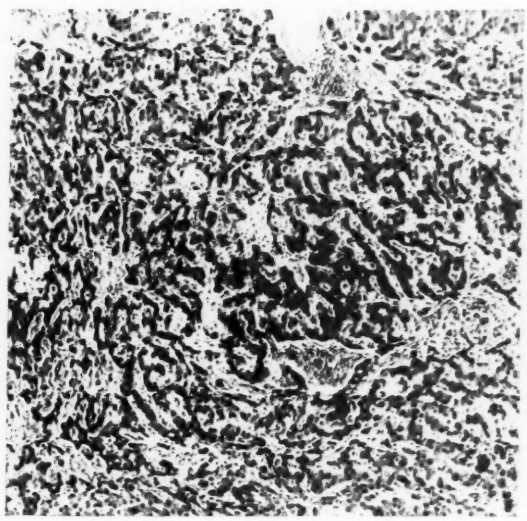

FIGURE III.

Photomicrograph showing biliary cirrhosis secondary to carcinoma of common hepatic duct—Case II. (*Haematoxylin and eosin stain.* × 50.)

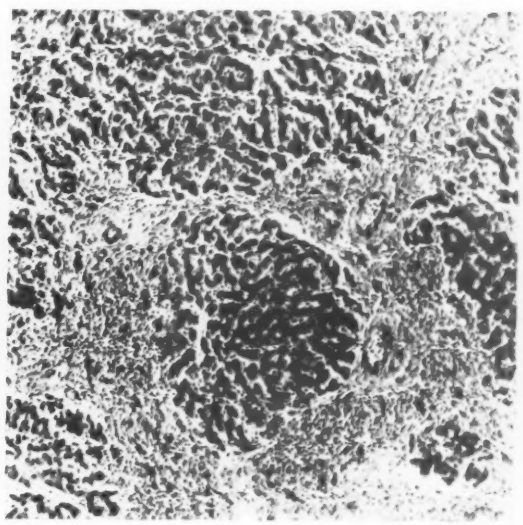

FIGURE VI.

Photomicrograph showing biliary cirrhosis secondary to adenocarcinoma of left hepatic duct—Case III. (*Haematoxylin and eosin stain.* × 50.)

ILLUSTRATIONS TO THE ARTICLE BY W. V. MACFARLANE

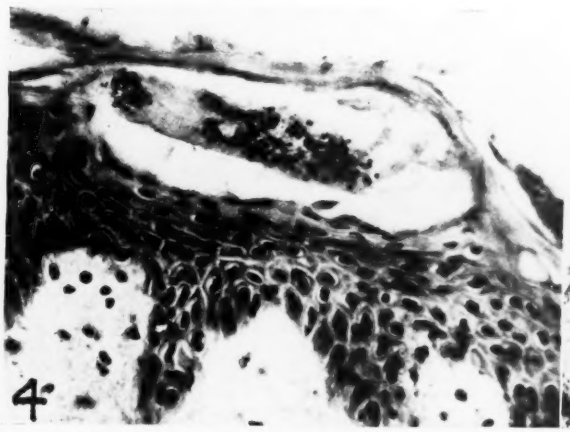

FIGURE IV.

Cercaria in the epidermis of a previously unexposed subject, twenty-four hours after invasion. Very little tissue reaction or cercarial damage is evident. (× 220.)

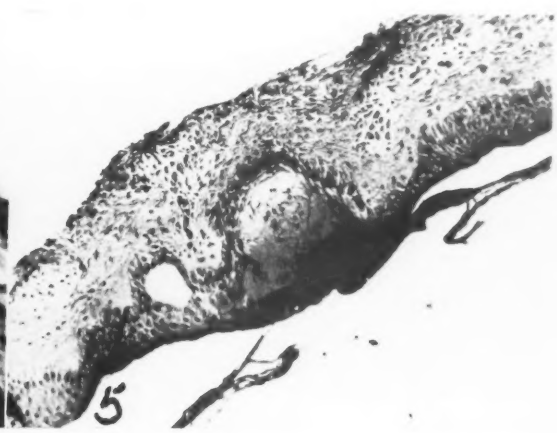

FIGURE V.

Cercarial burrow at thirty hours after invasion of a heavily sensitized subject. The cercaria has undergone lysis, there is pericellular oedema, and a vesicle full of protein exudate and neutrophile leucocytes is seen to the left of the burrow. (× 50.)

ILLUSTRATIONS TO THE ARTICLE BY JAMES A. BONNIN.

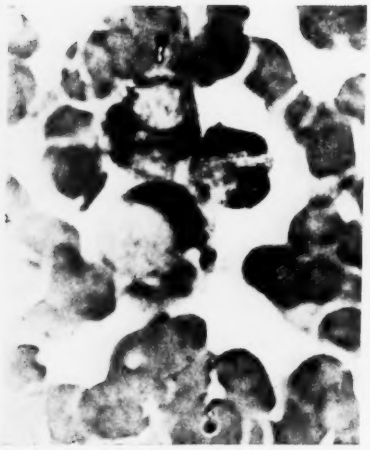

FIGURE I.

A small cluster of L.E. cells. One has two inclusion bodies. (× 1250.)

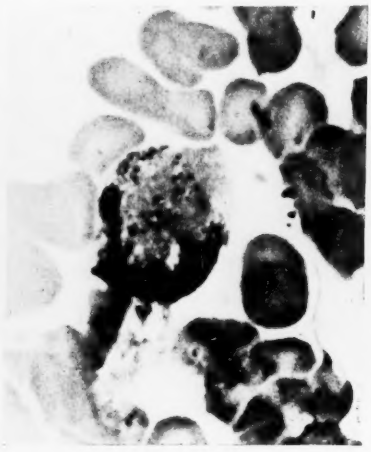

FIGURE II.

A single L.E. cell. (× 1250.)

FIGURE III.

The origin of the inclusion bodies and production of L.E. cells. The degenerating nucleus of a polymorphonuclear leucocyte is shown at the bottom. Two fine threads of nuclear material extend upwards from it and are almost in continuity with each of two free, homogeneous masses derived from other lobes of that nucleus. A normal polymorphonuclear leucocyte is in the process of phagocytosing the homogeneous mass on the right. Two complete L.E. cells appear above. (× 1250.)

ILLUSTRATIONS TO THE ARTICLE BY RICHARD FLYNN.

FIGURE I.

FIGURE II.

FIGURE III.

lesions are not usually found with biliary cirrhosis secondary to cholangitis or to extrahepatic biliary obstruction is that the stimulus is either intermittent or of insufficient duration (for example, the patient who dies of carcinoma of the head of the pancreas before the serum lipid levels have risen sufficiently to induce xanthoma formation). This concept is in accord with McMahon and Thannhauser (1949), who now reject the original hypothesis that xanthomatous biliary cirrhosis is due to an abnormality of cholesterol metabolism with xanthomatous deposits in the biliary tree causing obstructive cirrhosis (Thannhauser and Magendantz, 1938). Primary biliary cirrhosis is therefore an uncommon condition, characterized clinically by a prolonged course, with hepatomegaly and intrahepatic obstructive jaundice, and by a tendency to xathoma formation; diagnosis during life can be made only by exclusion of extrahepatic biliary obstruction by laparotomy.

In 1950 the Gastro-Enterological Unit at this hospital had the opportunity to investigate in consultation two cases which seemed to conform to the clinical criteria for diagnosis of primary biliary cirrhosis. The subjects were two adult males who had had prolonged obstructive jaundice with hepatomegaly and in whom laparotomy had revealed no abnormality, and liver biopsy had revealed early biliary cirrhosis; and yet both subjects came to autopsy, at which primary carcinoma of the bile ducts giving rise to organic intrahepatic biliary obstruction was found.

CASE II.—H.H., a male patient, aged sixty years, an invalid pensioner, was admitted to hospital on February 10, 1950. His previous health had been good, except that since the age of twenty years he had been incapacitated by a muscular dystrophy characterized by symmetrical weakness and muscular wasting in all four limbs, with predominantly proximal distribution, pronounced weakness of the shoulder girdle muscles, winging of the scapulæ and weakness of the spinal muscles, so that the patient could not stand up, after having bent down, without supporting himself with his hands on his thighs; there were wasting of the sternomastoids and a bird-like facies; testicular sensation was absent; cataracts were not present, although slit-lamp examination was not performed; there was no myotonia. The family history was free from abnormality as regards both similar disability and the presence of cataracts. There had been no change in the general condition of the patient for many years, and he stated that he had been in good health until late July, 1949. At that time the patient noticed jaundice for the first time, which was associated with pale stools and generalized itching. There was no abdominal or back pain or discomfort. The degree of icterus gradually increased, although the patient experienced no disability other than intolerable pruritus. He was admitted to a suburban hospital on September 8, 1949, where physical examination revealed no gross abnormality other than deep jaundice and clay-coloured stools. A provisional diagnosis of carcinoma of the head of the pancreas was made, and laparotomy was performed on September 23. The gall-bladder was found to be normal in size and did not contain calculi; no abnormality could be found in the pancreas, stomach or duodenum; the extrahepatic biliary tree appeared normal, and exploration of the common bile duct revealed no obstruction. A cholecystduodenostomy was performed. The patient convalesced satisfactorily and was discharged from hospital on October 13, without any apparent change in his clinical condition.

He remained continuously icteric with pale stools and pronounced itching, but otherwise well, until late in January, 1950, when for the first time he noted some anorexia, and the fact that his weight had fallen by four pounds to eight stone six pounds. He was admitted to the Royal Prince Alfred Hospital on February 10, 1950. On examination of the patient there was deep jaundice, and the liver was enlarged one inch below the right costal margin; it was firm, smooth in contour and non-tender. The spleen was not palpable. No masses or tenderness could be detected on examination of the abdomen, but the previous laparotomy incision was extremely indurated. No ascites could be detected. There were no spider nævi or skin xanthomata, nor was palmar erythema present. Apart from the muscular dystrophy already noted, the remainder of the physical examination gave normal findings. No fever was present. The stools were clay-coloured. Laboratory investigations gave the following information: cells numbered 4,150,000 per cubic millimetre, the hæmoglobin value was 11·4 grammes *per centum*, the total and differential leucocyte counts were within normal limits, the serum bilirubin level was 30 milligrammes *per centum*, the total serum protein content was 6·9 grammes *per centum*, the serum alkaline phosphatase content was 52·5 King-Armstrong units, the thymol flocculation test produced a negative result and the prothrombin index was estimated at 63%.

On February 15, 1950, a second laparotomy was performed. The abdominal wall at the site of the previous laparotomy was extensively calcified. The cholecyst-duodenostomy was found to be functioning perfectly; no abnormality could be detected in the pancreas; the extrahepatic biliary tree was normal; the *porta hepatis* was carefully palpated and found to be normal. The liver was enlarged and appeared to be finely cirrhotic; a biopsy specimen was taken from the right lobe. No extrahepatic biliary obstruction could be found and the abdomen was closed. Operation liver biopsy revealed that the connective tissue in the portal tracts was increased in amount and contained more cells than usual including polymorphonuclear leucocytes. Some of the liver cells surrounding the central veins of the lobules were obviously degenerate, and at this site there were also small collections

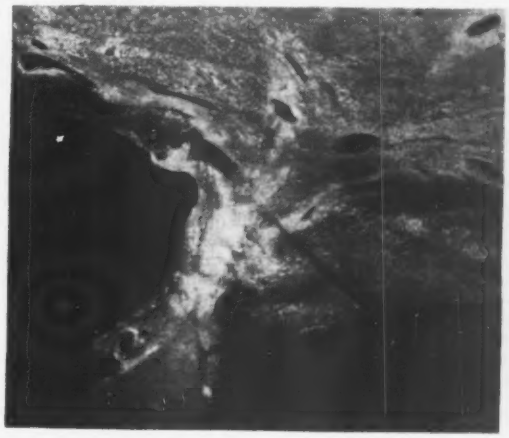

FIGURE II.

Photograph showing intrahepatic carcinomatous stricture of the common hepatic duct. Portion of the liver has been cut away. (Case II.)

of polymorphonuclear cells. Regeneration of liver cells was observed. Intralobular plugging by bile was seen in some lobules. The pathologist (Dr. V. J. McGovern) considered that the specimen had all the criteria for cirrhosis, but on a minor scale.

The patient's convalescence from the operation was satisfactory, but there was no change in his condition. Jaundice increased in intensity and was associated later with skin pigmentation. Itching was as intractable as previously, and the stools remained acholic. The general condition of the patient was well maintained until late in March, 1950, when deterioration in appetite occurred. Biochemical investigations on March 30, 1950, gave the following information: the serum bilirubin content was 54 milligrammes *per centum*, the serum alkaline phosphatase content was 55·8 King-Armstrong units, the thymol flocculation test produced a negative result, the total serum protein content was 7·2 grammes *per centum*, and the total blood cholesterol content was 560 milligrammes *per centum*. Towards the second week in April it was shown that the patient's condition was deteriorating; his appetite was poor, he had lost weight and he felt too weak to get out of bed. There was no gross change in the physical signs, the liver had not enlarged further, and there was no splenomegaly, ascites or peripheral œdema. No xanthomata were seen, and fever remained absent. The patient finally became lethargic, was semicomatose for two days and died on April 17, 1950.

An autopsy was performed by Dr. V. J. McGovern. All organs were grossly bile-stained. The pleural cavities were normal. Examination of both lungs (right 535 grammes, left 530 grammes) revealed well established bronchopneumonia in the lower lobes. In the pericardium early fibrinous pericarditis was apparent, with early adhesions between the anterior surface of the heart and the parietal pericardium.

In the heart (300 grammes) no gross abnormality was detected. There was no atheroma of the coronary vessels, and in the aorta only a minimal amount of atheroma was present. The peritoneal cavity did not contain free fluid. In the spleen (205 grammes) normal architecture was present, but it contained numerous large foamy histiocytes, some containing pigment. The brain and spinal cord were normal on macroscopic and microscopic examination; the cerebrospinal fluid was bile-stained. In the kidneys (right 178 grammes, left 182 grammes) no abnormality was detected. All other organs were normal; the testes were not examined microscopically. The pancreas was normal and the extrahepatic biliary tree was normal except for a patent cholecystduodenostomy. The liver weighed 1500 grammes and was deep green in colour, and its surface exhibited a fine granularity. On section, the bile passages were grossly dilated and contained pale yellow bile. On further section through the *porta hepatis*, which appeared normal from outside, stenosis of the common hepatic duct was seen within the *porta hepatis*, which virtually occluded the lumen (Figure II). On section this apparently benign stricture had the microscopic picture of an early duct carcinoma. Microscopic examination of the liver parenchyma revealed biliary cirrhosis (Figure III), showing generalized increase in portal connective tissue; the liver lobules showed degeneration and regeneration of liver cells. Plugging with inspissated bile was not a pronounced feature, small bile duct epithelium was not prominent, and there was very little in the way of accumulation of inflammatory cells.

This case of prolonged jaundice was thought at one time possibly to be due to a functional disturbance of the liver, similar to primary biliary cirrhosis. The jaundice was obstructive in type both clinically and biochemically; but two careful laparotomies had failed to find any extrahepatic biliary obstruction. The liver was enlarged and early cirrhotic changes were found by operation biopsy. There was no clinical or biochemical evidence of liver failure, and the blood cholesterol level was greatly elevated, although no xanthomatous formations were evident. The course was prolonged without great constitutional disturbance until the patient died nine months after the onset of jaundice, rather quickly, with terminal bronchopneumonia. Autopsy revealed primary carcinoma of the common hepatic duct within the *porta hepatis*, occluding the lumen, without local or general metastases. The *porta hepatis* was normal to inspection and palpation before the liver was cut. The intrahepatic division of the common hepatic duct must represent an anatomical variant. The calcification in the first abdominal wound is not satisfactorily explained.

A second case, very similar in some ways, but somewhat more complicated, was investigated at the same time.

CASE III.—F.K., a male subject, aged forty-eight years, an automobile mechanic, was admitted to hospital on January 25, 1950. His previous health included an attack of pleurisy in 1934, and he had complained of an intermittent non-productive cough for several years. His normal weight was 14 stone eight pounds. The patient gave the story that his illness had commenced in June, 1949, with early morning nausea and sometimes vomiting after breakfast, associated with some mild general diminution in appetite, although not of severe degree. This state of affairs continued without change until September, 1949, when he noticed that his urine was dark in colour and his stools were pale, and this condition was succeeded by obvious jaundice and itching of the skin later in the month. He was admitted to the Repatriation General Hospital, Concord, on October 19, 1949, for investigation, having had jaundice for three weeks. There had been no pain or discomfort in the abdomen or back. On examination of the patient pronounced jaundice was noted; the liver was palpated just below the right costal margin, it was firm, smooth and non-tender, and the spleen was impalpable. There were no enlarged lymph glands. Ascites and ankle œdema were absent, and the rest of the physical examination revealed no significant abnormalities. The stools were pale. Laboratory investigations gave the following information: the hæmoglogin value was 16 grammes *per centum*, the total and differential leucocyte counts were within normal limits, the serum bilirubin content was 17·6 milligrammes *per centum*, the serum alkaline phosphatase content was 46·8 King-Armstrong units, the blood cholesterol content was 263 milligrammes *per centum*; the urine contained bilirubin, but no abnormal quantities of urobilin or urobilinogen. A plain X-ray film of the abdomen revealed no opaque calculi, and a barium meal examination did not reveal any abnormality of the œsophagus, stomach or duodenum. An X-ray examination of the chest showed a pronounced increase in the lung markings and the reticular pattern, particularly on the left side, with a faintly nodular appearance. While undergoing these examinations the patient remained icteric and complained of itching and some nausea, his stools were pale and he had an irregular temperature up to 101° F. Obstructive jaundice, probably due to carcinoma of the head of the pancreas, was the clinical diagnosis, and a laparotomy was performed on November 10. At operation the gall-bladder was found to be normal and contained no stones. The stomach, duodenum and pancreas appeared to be normal. The common bile duct was opened and explored, but no abnormality could be detected. The *porta hepatis* was palpated and appeared normal; the liver itself was enlarged, although not grossly, and a biopsy specimen was taken from the left lobe. No extrahepatic biliary obstruction could be found, and the abdomen was closed without any further surgical procedure being performed. The operation liver biopsy revealed a slight increase in the periportal connective tissue and a moderate amount of periportal inflammatory infiltration. There was evidence of both degeneration and regeneration in liver cells. Bilirubin staining of the centrilobular liver cells and bile plugging were pronounced; it was considered probable that the patient was suffering from cholangiolitic hepatitis. The patient's post-operative convalescence was uneventful; his fever subsided, although he remained as deeply icteric as previously and still complained of severe itching. He was discharged from hospital on December 21, 1949.

The patient remained in approximately the same state of health, with jaundice, pruritus, pale stools, some anorexia and nausea, and without fever, until his admission to the Royal Prince Alfred Hospital on January 25, 1950. It was noted that he had lost weight from his normal figure of 14 stone eight pounds to 12 stone two pounds. On examination of the patient, jaundice was deep and there were no xanthomata, liver palms or spider nævi. The liver appeared to be enlarged three inches below the right costal margin, smooth and firm, but tender. The spleen was not palpable. There was no ascites or pitting œdema of the ankles. There were no other abnormal physical signs. The stools were pale and the urine contained bile pigments to ward (iodine) testing. Laboratory investigations gave the following information: the serum bilirubin content was 18·5 milligrammes *per centum*, the serum alkaline phosphatase content was 36 King-Armstrong units, the thymol flocculation and serum Lange tests both produced negative results. The patient was treated with bed rest and dietary supplements. For the next ten weeks the patient had a continuous irregular temperature up to 101° F., he complained of increasing anorexia and nausea and of severe pruritus, and his weight dropped further to 10 stone two pounds. The liver appeared to enlarge gradually until it was five inches below the right costal margin; it remained tender. The spleen was always impalpable. No ascites was evident, but œdema of the ankles was noted at the end of this period. The stools were pale and later became acholic. Laboratory investigations during this period revealed leucocytosis, up to 18,000 leucocytes per cubic millimetre, 84% being polymorphonuclear cells. The patient had short courses of penicillin and streptomycin without apparent change in his general condition, in the height of the fever or in the degree of leucocytosis. There was progressive anæmia, although examinations of the stool for occult blood gave consistently negative results, and a blood count on April 7 showed the red cells numbered 2,600,000 per cubic millimetre; the hæmoglobin value was 9·4 grammes *per centum* (some macrocytosis being evident in the smear); the mean corpuscular volume was calculated at 103 cubic μ, but free acid was detected in the gastric juice and examination of a sternal marrow smear revealed active erythropoiesis of the normoblastic type. During this period the jaundice tended to vary a little in intensity, the serum bilirubin content ranging from 18 to 32 milligrammes *per centum*, although towards the end of the period the jaundice remained consistently deep. The blood cholesterol values varied from 240 to 280 milligrammes *per centum*, and no skin xanthomata became manifest. The serum alkaline phosphatase level varied between 36 and 50 King-Armstrong units, but the thymol flocculation and serum Lange tests results always remained negative. The total serum protein level fell to 5·7 grammes *per centum* with an albumin-globulin ratio of 1·1: 4·6.

During the first week in May, 1950, it was noted that what had been taken to be the tender liver, increasing in size, was fluctuant, and on May 13 four and a half pints of bile and blood-stained pus were aspirated from a large subhepatic abscess, and a rubber drainage tube was inserted, which

continued to discharge bile for two weeks. After this procedure the fever subsided, the jaundice declined somewhat and the stools regained a little colour. However, the patient continued to lose ground despite blood transfusion, complained of itching and almost total anorexia, and his weight declined to nine stone eight pounds. On May 28 a second diagnostic laparotomy was undertaken, and it was found that the now-collapsed subhepatic abscess communicated with an even larger cavity containing pus, blood, bile and necrotic debris, and the general appearance suggested the possibility of an amœbic abscess of the liver, although earlier investigations on the stools and colon had not lent any support to an amœbic basis. It was impossible to do anything further than to drain the large abscess. Section

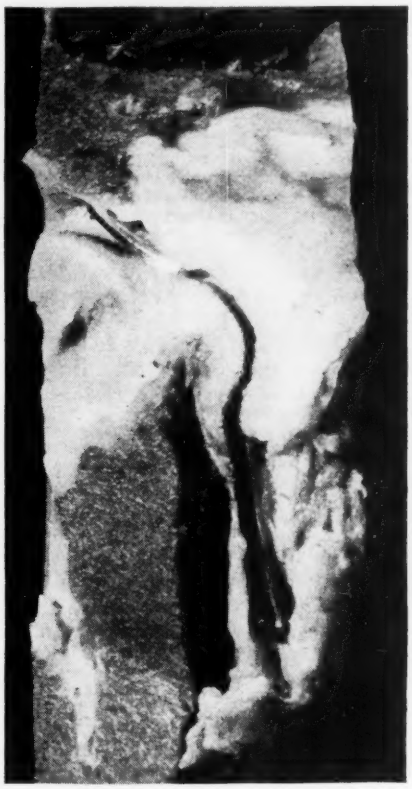

FIGURE IV.

Photograph showing intrahepatic adenocarcinoma of the left hepatic duct with local infiltration (Case III).

of the wall and examination of the pus did not support the diagnosis of tropical abscess, non-specific granulation tissue and hæmolytic *Staphylococcus aureus* being found. After this procedure the temperature remained normal and the jaundice receded remarkably, so that on June 8 the serum bilirubin content was estimated at 9·5 milligrammes *per centum*. However, the tube within the abscess cavity continued to drain copious amounts of bile-stained pus, and the patient gradually lost ground and died a cachectic death on June 23 despite chemotherapy.

At autopsy (Dr. V. J. McGovern) there was pronounced bile staining of all organs. Both pleural cavities contained old adhesions. Examination of the right lung (413 grammes) showed no obvious abnormality. In the left lung (813 grammes) scattered nodules of abnormal tissue were found, peribronchial in distribution, which tended to conglomerate in the lower lobe, and microscopically these proved to be areas of lipoid pneumonia in which fibrosis had commenced. In the heart (257 grammes) no abnormality was detected; there was no coronary atheroma. The spleen (170 grammes) was normal. The other viscera except those described below were normal. Examination of the peritoneal cavity showed that the two abscess cavities had collapsed and that there was a fair amount of adherence between the abscess walls and the neighbouring viscera. The abscess cavities did not communicate with the liver substance and were totally subhepatic. There was pronounced plastic pelvic peritonitis; loops of small intestine were densely adherent to the floor of the pelvis in which loculated abscesses were found. The stomach, duodenum and pancreas were normal, the gallbladder was normal and in the extrahepatic biliary tree no abnormality was found. The liver weighed 2220 grammes and was green in colour. The *porta hepatis* was normal on external appearance. On section of the liver a carcinoma was found arising from and obstructing the left hepatic duct within the liver (Figure IV). It measured two centimetres in diameter. There was spread of the carcinoma into the left lobe of the liver, but this was not extensive. This proved to be adenocarcinoma on microscopic examination. In the left lobe of the liver an abnormality in architectural pattern was found as compared with the right lobe and considerable ectasia of the bile ducts (Figure V). On microscopic examination of the liver parenchyma of the left lobe, biliary cirrhosis was present. Lobules were

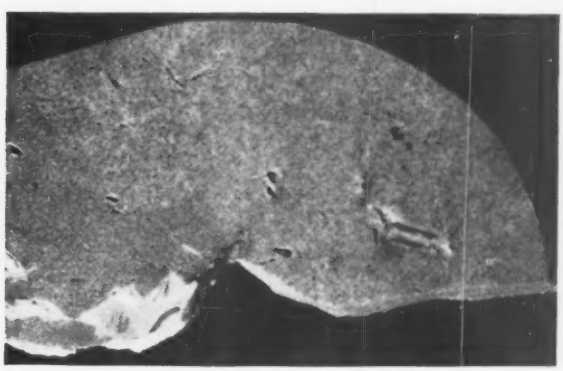

FIGURE V.

Photograph showing biliary cirrhosis of the left lobe of the liver secondary to carcinoma of the left hepatic duct only. The right lobe of the liver is normal. (Case III.)

diminished in size and the connective tissue in the portal tracts was greatly increased and showed a pronounced inflammatory reaction, although there was little evidence of bile duct proliferation. In the centres of the lobules pronounced bile staining was evident, and the bile ducts in the portal tracts showed prominent bile plugging (Figure VI). The histological picture of the liver parenchyma from the right lobe was normal.

This patient presented with painless jaundice of obstructive type, in which laparotomy revealed no extrahepatic biliary obstruction, and in which operation liver biopsy from the left lobe revealed changes interpreted as hepatitis; treatment was medical. The case was complicated by large post-operative subhepatic abscesses, which obscured the clinical picture and played a large part in the patient's cachectic death. Throughout the nine months' course there was no evidence, either clinical or biochemical, of gross hepato-cellular failure, except late hypoproteinæmia and reversal of the albumin-globulin ratio. The picture resembled primary biliary cirrhosis and the large subhepatic abscess for a long time suggested the hepatomegaly typical of that condition. A point of difference was the absence of rise in blood lipid level and the absence of skin and other xanthomata. At autopsy the prime lesion was found to be a totally intrahepatic primary adenocarcinoma of the left hepatic duct, with secondary biliary cirrhosis of the left lobe of the liver only. Two points of interest arise. The first is that biliary obstruction was never complete, except perhaps for a short period when the subhepatic abscess was at its largest (the serum bilirubin level fell considerably after the two drainage operations). This will have accounted for the fact that the stools were not completely acholic for the major part of the illness, and it may also have accounted for the rela-

tively normal blood cholesterol levels and for the absence of xanthomata. The second point of interest is that, as the lesion involved the left hepatic duct and caused secondary biliary cirrhosis of the left lobe of the liver only, had an aspiration liver biopsy been carried out during the course of the illness to assess the progress of the hepatitis, only tissue from the normal right lobe would have been obtained. The presence of lipoid pneumonia is unexplained.

Both cases represent chronic obstructive jaundice with totally negative laparotomy findings, in which the diagnosis of primary biliary cirrhosis was entertained, and in which the final diagnosis was proved to be carcinoma obstructing the intrahepatic bile ducts. It will be noted that in each of the foregoing cases, even at autopsy, no abnormality could be noted in the *porta hepatis* before the liver was cut, so that absolute diagnosis by laparotomy alone would have been impossible.

The two last cases are presented to show the difficulty in the diagnosis of primary biliary cirrhosis or chronic "non-surgical" intrahepatic obstructive jaundice, when hepatomegaly is associated with jaundice, clinically and biochemically obstructive in type, when laparotomy shows no extrahepatic biliary obstruction, and when biopsy of the liver reveals biliary cirrhosis and there is no evidence of ascending cholangitis.

Discussion.

Whereas primary biliary cirrhosis is a rare disease, primary malignant tumours of the large bile ducts are not uncommon, being at least as common as primary carcinoma of the gall-bladder in some series (Willis, 1942; Kirshbaum and Kozoll, 1941). Since the publication of the first large group of 90 cases by Rolleston (1912) several reviews of further series have been documented (Shapiro and Lifvendahl, 1931; Judd and Gray, 1932; Marshall, 1932; Stewart *et alii*, 1940; Kirshbaum and Kozoll, 1941; Neibling, Dockerty and Waugh, 1949). These neoplasms are to be differentiated from malignant cholangiomata arising from cholangiolar epithelium within the liver, and sometimes of multiple origin. Histologically the tumours are mainly infiltrating adenocarcinomata, less commonly scirrhous, and more rarely (10%) papillary in type. In some cases (as in Case II) a small localized annular stenosing growth may be present, which may be mistaken for simple cicatrization at laparotomy or autopsy unless it is microscopically examined (Willis, 1942). The site of primary growth is localized to the common hepatic or single hepatic ducts in approximately 20% of all cases. Obstructive jaundice, often with hepatomegaly and progressive weight loss, is the main clinical feature. Ascites is frequent. Biliary cirrhosis and in some cases hydrohepatosis are common accompanying features; biliary cirrhosis was demonstrated at autopsy in 51 of 62 cases of carcinoma of the extrahepatic bile ducts in one series (Kirshbaum and Kozoll, 1941). Death is usually due to a combination of factors—cachexia, cholæmia and bronchopneumonia. In a review of 35 cases of carcinoma of the hepatic ducts Stewart *et alii* (1940) commented on the fact that at autopsy in only 17 was there evidence of extension of the lesion (to the liver and regional lymph nodes), and that in 26 cases the original tumour was extremely localized; they concluded that the tumours were small and slowly growing and metastasized late. Despite this, all patients were dead within one year of the onset of jaundice, with an average duration of illness of six and a half months.

However, none of the reviews have drawn specific attention to the syndrome exhibited in the two cases reported above—namely, obstructive jaundice and biliary cirrhosis with negative laparotomy findings in the presence of carcinoma of the hepatic ducts—although Stewart *et alii* (1940) record that laparotomy was performed in 21 of 35 cases, but a lesion was detected in only 16. In one unreported case of Klatskin, quoted by Ahrens, Kunkel *et alii* (1950), in which biliary cirrhosis and xanthomatosis were present, autopsy revealed an adenocarcinoma of the hepatic duct junction despite negative findings at two laparotomies. In a further case reported by Sherlock (1951) of chronic obstructive jaundice, biliary cirrhosis (by biopsy) and xanthomata, after two laparotomies autopsy revealed scirrhous carcinoma of the intrahepatic bile ducts, although at the second laparotomy a mass was said to have been palpable in the *porta hepatis*.

Conclusions.

It would appear that negative findings at laparotomy and exploration of the extrahepatic bile ducts in cases of obstructive jaundice do not necessarily imply that the jaundice is due to an abnormality of function of the liver parenchyma, even if histological examination reveals evidence of biliary cirrhosis. Although surgery has as yet little to offer in cases of intrahepatic bile duct carcinoma, the differentiation between this condition and that of primary biliary cirrhosis may have a clinical bearing in regard to prognosis. Whereas in hepatic duct carcinoma the average time of survival was six and a half months from the onset of jaundice and the maximum time was one year in the series of 35 cases (Stewart *et alii*), in cases of primary biliary cirrhosis, although the illness proved fatal in two years in some cases, other patients are still alive after eleven years of jaundice (Ahrens, Kunkel *et alii*). On the other hand, in the case quoted by Sherlock (1951) four years elapsed between the time of onset of jaundice and death, and in the two cases reported here the duration of illness was nine months in each case and death was due to bronchopneumonia in the first and to local and generalized peritonitis in the second. It would appear probable that in these two cases cholangiography at the time of the original negative laparotomy findings in each instance might have clarified the diagnosis. It is suggested, therefore, that in a case presenting as obstructive jaundice, in which laparotomy reveals no extrahepatic obstruction even though the liver may show cirrhotic changes before the diagnosis of primary biliary cirrhosis or hepatitis is made, a cholangiogram should be taken at operation with the object of outlining the main intrahepatic bile ducts, to exclude the presence of a space-occupying lesion blocking the large bile ducts within the liver substance.

Summary.

1. Intrahepatic biliary obstruction is mentioned as a useful clinical conception to explain certain features during acute hepatitis.

2. A case is reported of infective hepatitis with a somewhat prolonged course, which presented certain features of obstructive jaundice during the patient's recovery.

3. Cases of more prolonged jaundice of obstructive type are mentioned, and the clinical and biochemical features of primary biliary cirrhosis are described.

4. Two cases of prolonged jaundice with certain features suggesting primary biliary cirrhosis are reported, in which the autopsy findings were of intrahepatic carcinoma of the main bile ducts associated with biliary cirrhosis, to show the difficulty in making the diagnosis of primary hepatic disease in cases of prolonged jaundice with obstructive features, in which no extrahepatic obstruction can be found at laparotomy.

5. It is suggested that the exclusion of an organic intrahepatic bile duct obstruction should be attempted by cholangiography at laparotomy before a diagnosis of primary biliary cirrhosis is made.

Acknowledgements.

I wish to thank Dr. A. W. Morrow, physician in charge of the Gastro-Enterology Unit, Royal Prince Alfred Hospital, for permission to publish the case reports contained herein; Dr. V. J. McGovern, morbid anatomist, Fairfax Institute of Pathology, for the pathological material and reports; and Mr. S. Woodward-Smith, Department of Medical Artistry, University of Sydney, for the photographs.

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SCHISTOSOME DERMATITIS IN AUSTRALIA.

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BATHERS in lakes in Western Australia and in river shallows along the Murray have periodically been attacked by cercarial parasites which produce an allergic skin lesion. This type of lesion was ascribed by Cort (1928), in Michigan, to schistosome invasion. Reports of this type of dermatitis have come from America (Cort, 1936), Britain (Matheson, 1930), Europe (Brumpt, 1931), South Africa (Porter, 1931), Australia (Johnston, 1941) and New Zealand (Macfarlane, 1944), and different species of the Schistosomatidæ have been shown to be involved in each country.

The adult trematodes mature in the mesenteric veins of water birds, and the intermediate stages are developed in pulmonate snails. Cercariæ released from these snails would normally invade duck or other birds, but they able to secrete proteolytic enzymes which allow penetration of the human skin. The substances released from the parasites cause the formation of antibodies in the skin, and subsequent invasion by cercariæ results in an itching red reaction (Macfarlane, 1944).

In Australia, Harvey Johnston (1941) described the itch and surmised that *Cercaria parocellata* might, on morphological grounds, be the parasite involved.

A further investigation was undertaken during the past two summers to determine the responsible organism and its distribution in Australia, as well as to study the skin reactions to cercarial antigens.

[1] Work undertaken with the aid of a grant from the National Health and Medical Research Council of Australia.

Distribution in Australia.

The original reports of Australian schistosome dermatitis came from the Murray Valley swamps (Johnston, 1939). In the present survey reports of the itch were obtained at Albury, Birri, Loxton, Mannum, Murray Bridge and Tailem Bend. At all of these places the river spreads into shallows which allow the molluscan hosts to build up a population in close proximity to water birds. The main sufferers from itch are either those who bathe in the shallows and swamps rather than in the main river (Figure I) or those who are immersed while duck shooting. The paddling of shooting craft by hands leads to infestation up to the elbows. In recent years there has been little trouble, but there is a

FIGURE I.

Swamp water, two feet deep, on the west bank of the Murray River, three miles north of Mannum. The host molluscs floated on the debris to the left.

rough correlation between low river levels and high levels of infestation with cercariæ. The last series of low water years ended in 1948, and there has been little parasitization since that year.

In Western Australia a set of brackish lakes has formed in a former watercourse of the Wagin region. The largest lake, Dumbleyung, is 12 miles long, and was six to ten feet deep in 1950. Several of the other affected lakes were dried out by 1951, and the swimmers' itch had almost disappeared. During 1947, however, Wagin, Parkeyerring, Quarbing and Norring lakes were associated with the covering of hundreds of summer bathers with papular dermatitis. By 1950 most of the lakes had evaporated to 1% to 3% salt concentration, and only in Dumbleyung was dermatitis acquired, since its size and depth prevented high salt concentration.

At Narrabeen, near Sydney, in the summer of 1946-1947, bathers in the lake suffered a skin itch, which in some cases was associated with papular lesions. Some bathers in salt water reported a papular dermatitis. The Narrabeen lake water was relatively fresh at this time and may have carried schistosomes, but there has been very little,

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if any, infestation since 1947, according to the local practitioner who made the original observations. Marine forms of cercariasis are reported from the United States (Cort, 1950).

It is possible that other regions are affected, and any reports of infestation will be appreciated if transmitted to the author.

Parasites.

Examination of molluscs from infested waters yielded large numbers of species of cercaria—at least 11 species in Western Australia and nine from the Murray region. Of the four types of schistosome cercaria encountered, only one, *Cercaria parocellata*, penetrated the skin to produce experimental lesions. All the other species were tested on susceptible skin, and while one species of Western Australian heterophyoid cercaria induced a prickling sensation, it did not produce a papule. No other organism invaded the skin.

The host snail for *Cercaria parocellata* is *Limnæa lessoni* (Figure II), which has a wide distribution in Australia, occurring along most of the Murray swamps as well as in Western Australia. The infested lakes in the west were, however, almost entirely free of *Limnæa lessoni* in 1950.

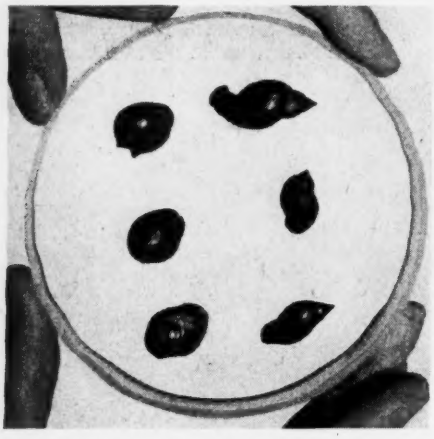

FIGURE II.

To the left are specimens of *Limnæa lessoni* (right hand spiral). This pulmonate is the host for *Cercaria parocellata*. To the right is *Lenameria pyramidata* (left hand spiral), the host for *C. jænschi*, which does not invade human skin.

Instead they carried a dense population of *Hydrococcus graniformis*. It was from this mollusc that the heterophyoid cercaria was obtained. At present it is not clear whether the hosts and parasite involved in Western Australian swimmers' itch are the same as those in the Murray. *Limnæa lessoni* does, however, occur in the Wagin region.

In the Murray River *Limnæa lessoni* lives in backwaters, often somewhat stagnant. When the water was hot and low in oxygen content the snails migrated on to rafts of swamp weed for oxygen, but they were apparently unaffected by the direct summer sun, which gave air temperatures over 90° F. This mollusc was not found in the fresh-flowing and better oxygenated shallows.

It is suspected that the black swan is the host for the adult schistosome in the Murray (Johnston, 1941).

Lesions.

Clinically three stages of infestation occur, and the course of the reaction depends upon the degree and time of previous exposure (Macfarlane, 1944; Olivier, 1949).

1. Previously unexposed subjects. When *Cercaria parocellata* is allowed to emerge from the mollusc and is contained in an adhesive plaster dam on the skin, a prickling sharp itch is experienced after about five minutes. This is caused by the digestion of the corneous and granular layers of the epidermis and the immigration of the body of the cercaria. The tail is shed at the skin surface. In some cases a macular vasodilatation appears after thirty to sixty minutes and persists for ten hours. In others no sign of the invasion is detectable. After five to seven days a slightly itchy papule forms at the site of invasion and lasts for three to five days before scaling off.

2. Previously exposed subjects. Cercariæ cause a prickling itch and may produce a transient red macule one millimetre in diameter. After ten to fourteen hours a delayed red papule appears and itches intermittently for two or three days. The papule may reach 1·5 centimetres in diameter and it lasts for five days.

3. Heavily reinfested subjects. The penetration itch is followed within ten minutes by the formation of a weal and axon reflex flare (Figure III). This accelerated papular response causes an intense histamine type of itch and lasts up to one and a half hours, then subsides. After

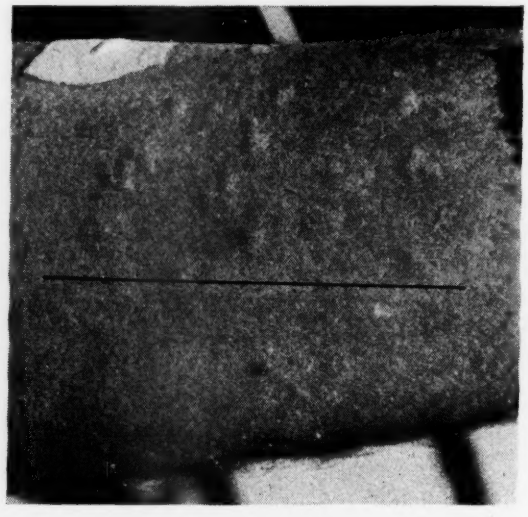

FIGURE III.

Accelerated papules, ten minutes after infestation of heavily sensitized subject by *Cercaria parocellata*, are shown above the line. These papules subsided in two hours and reappeared at nine hours. Below the line is an area simultaneously exposed to an unidentified schistosome cercaria from *Planorbis isingi*, with no evidence of invasion showing.

seven or eight hours a delayed papule with erythema and sometimes vesiculation appears, itches in a histamine fashion and lasts for seven days, though it is rarely troublesome after three days.

The course of events following natural infestation in Western Australia was much the same, except that the penetration itch was more intense and the lesions were smaller and of shorter duration than those acquired in the Murray.

Pathology and Immunology.

Some explanation of the various lesions may be offered in terms of biopsies taken at different stages and of antigenic responses obtained by injection of cercarial extracts.

1. Primary reaction. In unexposed subjects the cercaria penetrates, forming a burrow, and then dies (Figure IV). Biopsies of *Cercaria longicauda* show that the cercariæ slowly disintegrate over the course of seven days, while proliferation of the skin forms a parakeratotic plaque, which is shed after ten to fourteen days, and the plaque contains the remnants of the cercaria. During the first seven days of parasitization, intradermal injection of antigen made from *Cercaria parocellata* brings about a skin

reaction no different from that following an inert control injection. At the time when the papule forms, at the seventh day, an erythematous skin reaction to antigen may also be elicited. This indicates that about one week of delay after exposure is involved in antibody formation. The antibodies react with the residue of the cercariæ in the skin, at the seventh day, and produce a papule.

2. Secondary reaction. Subjects who have experienced a primary reaction follow a different course. Histologically it appears that *Cercaria parocellata* is destroyed in the skin between the twenty-fourth and thirtieth hours after penetration (Figure V), and by the forty-eighth hour an invasion of macrophages, small round cells and some eosinophile cells occurs. This cellular reaction is entirely absent from the primary invasion.

Antigen injected into a sensitized subject's skin brings on an erythematous itching response with a delay of four to six hours. The size of the erythema for *Cercaria longicauda* was found to be proportional to the degree of previous infestation (Macfarlane, 1949).

The secondary response is therefore an antibody-antigen reaction, followed by a leucocytic removal of the invader rather than a shedding of the cercaria, as in primary reactions.

In a highly sensitized subject a third type of change occurred. There was a double sequence of papule formations, one within the first hour of invasion and the second nine or ten hours later. This was investigated, *Cercaria parocellata* antigens being used. The cercariæ were filtered from a distilled water medium after two hours, and the cercarial residue was triturated. Filtrate and cercariæ were preserved with 1:10,000 "Zephiran" solution, and the mixture was made isotonic with human tissues by adding sodium chloride. Control solutions of water, preservative and mollusc washings were similarly prepared. In a highly sensitized subject the filtrate produced an early papule and flare, then after five hours a papule and erythema developed. The filtrate contains soluble products from the living cercariæ, comprising mostly the secretions of the penetration glands. It appears, therefore, that the early and late papular reactions do not require antigens from the whole organism. Since massively infested subjects develop this sequence, the accelerated reaction appears to be the result of prolonged exposure to cercarial products. It was thought that the early papule might be a specific response to the penetration enzymes, but the present experiments with antigens derived from penetration gland secretion indicate that this material can produce both accelerated and delayed phases of reaction. An acquired accelerated response to penetration substance antigens develops, and it resembles the initial skin reaction described for influenza virus by Beveridge and Burnet (1944).

Cercarial brei (0·05 millilitre given intradermally) caused, in this subject, an early papule, then a delayed papule surrounded by erythema 3·5 centimetres in diameter, whereas the filtrate showed only a two-centimetre erythema zone.

Cercaria longicauda antigen yielded responses equal to those from *Cercaria parocellata* in both mildly and severely sensitized subjects, the antibody levels giving areas of erythemata proportionate to the two sets of antigens, which must be chemically very similar.

Heterologous antigens prepared from *Cercaria jaenschi* (which does not invade human skin, although it is a schistosome cercaria) produced smaller and less persistent skin reactions than those following injection of *Cercaria parocellata* antigen.

Treatment.

The repellent properties of a 25% dimethyl phthalate cream[1] were tested in Dumbleyung, with the result that, in one experiment, 26 lesions appeared on the unprotected half of the body and two at the edge of the treated zone during one and a half hours. Ferguson *et alii* (1946) have shown that dimethyl phthalate offers good protection from human schistosomes, and Macfarlane (1949) used dimethyl phthalate (41%) effectively against *Cercaria longicauda*.

[1] Provided by Taylors Elliotts, Limited, Brisbane.

Once the secondary lesion has developed and the histamine itch is present, scratching may lead to rupture of the vesicle and bacterial invasion follows. It was found in 1947 (Macfarlane, 1949) that antihistamines give relief for four hours from the itch if applied as 2% or 3% solutions in *Unguentum Aquosum*. Although itch is relieved, the papule and erythema persist in spite of antihistamines.

Copper sulphate has been used to destroy snails in infested waters (Brackett, 1940; Macfarlane, 1949); for fresh water two or three feet deep an amount of six pounds per 1000 square feet of surface produces a lethal concentration. When the water is not flowing and is at the summer temperatures of 21° to 25° C., it is found *in vitro* that three or four parts of copper per million for thirty minutes kill 100% of *Myxas* and *Limnæa*. The effect of temperature on molluscacides has been analysed by Hoffman and Zakharz (1951); the necessary lethal concentration is found to decrease rapidly above 25° C. Brackish water, like that in the Western Australian lakes, would require more copper because of precipitation of the copper ion as insoluble hydroxycarbonate. On the other hand, the shallow warm water would increase the killing power of the ions.

Summary.

1. In Australia swimmers' itch occurs in the Wagin lakes of Western Australia and along the swamp waters of the Murray River. A similar parasitization is reported from near Sydney.

2. In the Murray region the organism concerned is *Cercaria parocellata* Johnston. The host pulmonate is *Limnæa lessoni*.

3. Primary non-allergic and secondary allergic lesions occur as a result of the invasion of the cercaria. In primary lesions antibodies appear after five to eight days, and the cercaria is extruded in desquamated epidermis. With secondary lesions tissue antibodies are present and papules appear in eight to twelve hours. The parasite is destroyed by leucocytes.

4. Hypersensitized subjects show during two hours after infestation an accelerated papular response. Cercarial secretion used as an antigen induces both accelerated and delayed papules.

5. *Cercaria parocellata* and *Cercaria longicauda* are antigenically similar, but *Cercaria jaenschi* behaves heterologously to give no accelerated response and a reduced delayed reaction.

6. Protection against invasion is given by dimethyl phthalate cream. Antihistamine cream alleviates the itching secondary lesions, but the papules remain.

Acknowledgements.

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L.E. CELLS IN THE PERIPHERAL BLOOD, WITH A REPORT OF A CASE OF ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS.

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ACUTE disseminated *lupus erythematosus* is uncommon in South Australia. It was therefore fortunate that such a case existed at the Royal Adelaide Hospital at the time when recent papers by Lee (1951) and by Lee, Michael and Vural (1951) appeared in the literature. In the first of these papers a very simple method of demonstrating the *lupus erythematosus* (L.E.) cell phenomenon was described and a greater sensitivity was claimed than with other methods. The case to be reported in this paper was not diagnosed until a pronounced remission had occurred, and attempts to demonstrate L.E. cells were repeatedly unsuccessful. On the first occasion when the test described by Lee was employed, L.E. cells were found in moderate numbers in a very short time. It is the purpose of this paper to add confirmation to Lee's work in regard to this simplified test and to give further support to his views on the origin of the inclusion bodies. A photograph is presented which demonstrates the production of inclusion bodies by the peculiar degeneration occurring in the nucleus of a polymorphonuclear leucocyte, together with their ingestion by other leucocytes.

Technique.

The test is performed on peripheral blood and no anticoagulant is used. Between one and two millilitres of venous blood are withdrawn into an autoclaved syringe and placed in a clean, dry test tube and allowed to clot. After one and a half to two hours at room temperature a portion of a wooden spatula is inserted into the tube and the clot is traumatized sufficiently to allow a considerable number of the entangled cells to escape into the surrounding serum. The remainder of the clot is taken out and discarded. The tube is then centrifuged at 1000 to 1500 revolutions per minute for two minutes, and the clear supernatant serum is either removed with a pipette or decanted. The deposit is usually found to have clotted again, but this is easily freed by gentle stirring, and smears are made from the sediment. The smears are stained with Jenner-Giemsa or any other stain which is satisfactory for the examination of blood films, and after being dried are covered with a thin film of oil. They are first examined at the periphery of the smear with the low-power objective lens and then with the oil-immersion lens.

Lee states that "this sediment consists mainly of red cells; chamber counts have shown the total leucocyte count rarely to be higher than 2000 per cu. mm."; but this number seems to depend upon the original leucocyte count and the amount of trauma applied to the clot. Individual L.E. cells and clusters, rosette formation and free homogeneous nuclear masses are all present in the smears. From a large number of preparations giving positive results Lee has found that a search of five minutes is usually sufficient and that there is at least one L.E. cell per 100 leucocytes. Two hundred to 300 leucocytes are counted before the examination is abandoned in "negative" cases.

Report of a Case.

The patient was a girl, aged twenty-three years, who had been ill for ten weeks prior to her admission to the Royal Adelaide Hospital. She complained especially of joint stiffness, of headache, and of the presence of painful, tender glands in the posterior triangle of the neck. Some days later a rash appeared on the buttocks and legs, and gradually spread over the whole of the body surface except the face, which was not involved until later.

One month after the beginning of her symptoms she noticed swelling of the ankles and hands, and soon afterwards she became severely ill with nausea, a persistent cough and a high pyrexia. She had been given sulphonamides, "Chloromycetin" and aureomycin without effect, and the onset of suprapubic pain, due to acute retention of urine, finally brought her to hospital.

On physical examination the patient was seen to be a flushed girl, obviously seriously ill, with a temperature of 101·4° F., a pulse rate of 100 beats per minute, very rapid respirations, photophobia and mental disorientation. Examination of the skin revealed a blotchy, red, erythematomacular rash over the thighs, most of the trunk and the upper extremities. The face was not involved at this stage. There was generalized enlargement of the lymphatic glands in the neck, axillæ and groins. The heart sounds were rapid, with a regular rhythm and a soft systolic bruit, maximal over the pulmonary area. The blood pressure was 130 millimetres of mercury, systolic, and 60 millimetres, diastolic. The apex beat was not palpable. The chest movements were a little greater on the right side than on the left, and signs of consolidation were present at the bases of both lungs. In the abdomen the liver was enlarged and the soft, lower edge was palpable two centimetres below the right costal margin. On inspiration, the spleen was palpable three centimetres below the left costal margin. The presence of an enlarged right kidney was detected one week after the patient's admission to hospital. There was difficulty in eliciting the right knee jerk, but other than this the cutaneous reflexes were normal.

The patient was admitted to hospital with the diagnosis of pneumonia; but there was such extensive involvement of so many tissues that acute disseminated *lupus erythematosus*, septicæmia and acute leuchæmia were considered the most probable diagnoses, with typhus fever and infectious mononucleosis as possibilities.

Investigations.

Investigations revealed the presence of erythrocytes, leucocytes and casts in the urine, with an occasional small amount of albumin; culture yielded a growth of coagulase-positive, hæmolytic staphylococci.

From the sputum a culture of coagulase-negative non-hæmolytic staphylococci was grown.

Hæmatological examinations gave the following information. The erythrocytes numbered 4,000,000 cells per cubic millimetre and the hæmoglobin value was 11·9 grammes per 100 millilitres; the volume of packed cells was 35%; the mean corpuscular hæmoglobin concentration was 34%; the platelets numbered 220,000 per cubic millimetre and the leucocytes 1500 per cubic millimetre. The latter consisted of 54% polymorphonuclear cells, 22% lymphocytes, 14% monocytes, 8% eosinophile cells and 2% basophile cells. The erythrocytes, leucocytes and plasma colour appeared normal. Direct eosinophile cell counts were never greater than 150 cells per cubic millimetre. The blood sedimentation rate was 90 millimetres in one hour (Westergren method). The serum proteins were estimated twice, with a more definite rise in the globulin fraction at the second examination. This

was as follows: the total serum protein content was 6·5 grammes per 100 millilitres, the serum albumin content was 1·7 grammes per 100 millilitres, the serum globulin content was 4·8 grammes per 100 millilitres, and the albumin-globulin ratio was 0·4 to 1·0. The serum agglutination tests gave negative results on each of three occasions, and the Wassermann test also produced a negative result. X-ray photographs of the chest revealed slight enlargement of the heart and heavy basal lung markings, suggesting inflammatory changes. The electrocardiographic tracing was within normal limits. Sternal marrow examination revealed no abnormality other than slight hyperplasia of the erythroid tissue.

After one week the patient's condition steadily began to improve, and it was not until the spontaneous remission was quite advanced that attempts were made to demonstrate the L.E. cell phenomenon. Both oxalated and heparinized plasma was mixed with marrow fluid from three other patients and from a normal rabbit, according to the techniques described by Berman, Axelrod, Goodman and McClaughry (1950). Another attempt was made by adding the oxalated L.E. plasma to the buffy coat removed from the peripheral blood of a subject of chronic lymphatic leuchæmia. In no case could L.E. cells be found, and it was not until the patient was almost free from all symptoms that the L.E. cells shown in the accompanying figures (Figures I to III) were demonstrated by the technique described. Suspicion was aroused when the oxalated L.E. plasma was mixed with aspirated marrow material from a subject of early pernicious anæmia, because the eosinophile granulocytes were found to have become phagocytic and contained ingested nuclear material. This material was probably lymphocytic in origin, and had not undergone the homogeneous structural change characteristic of the true L.E. cell. Such cells have been called "tart" cells by Hargraves *et alii* (1948). There was no phagocytosis observed in the smears made from a portion of this marrow which had not been mixed with the L.E. plasma. Similar findings occurred six days later when the plasma was mixed with the marrow aspirated from a patient suffering from lymphosarcoma, but it seemed to have no effect on the marrow cells of a normal rabbit and of a subject of multiple myelomatosis. The ability of L.E. plasma to produce phagocytosis has been often recorded, and has been shown by Haserick *et alii* (1950) to be due to the action of a specific globulin fraction which they have isolated.

Comment.

Lee *et alii* (1951) prepared smears from mixtures of known active L.E. plasma and normal leucocytes at one-minute intervals for five minutes, and noted the first significant changes which occurred in scattered polymorphonuclear leucocytes. After two minutes the nuclei of these cells were found to be swollen, had undergone the characteristic homogeneous change of the L.E. inclusion body and stained a similar reddish-purple colour. Either the whole nucleus or sometimes only one or more lobes were affected, so that the cells could still be identified as polymorphonuclear leucocytes. In later preparations free homogeneous masses were present, indistinguishable from the altered nuclei observed earlier.

Although this nuclear change and its subsequent phagocytosis have not been actually witnessed in wet preparations, the series of phases described above leaves little doubt as to the mode of production of L.E. cells. In Figure III the process is admirably demonstrated. At the bottom of the photograph the degenerated nucleus of a polymorphonuclear leucocyte can still be distinguished. Two fine threads of nuclear material can be seen extending upwards from it and are almost in continuity with each of two free homogeneous masses, representing two swollen lobes which have undergone this peculiar degenerative change. Two complete L.E. cells appear above these masses, while a third polymorphonuclear leucocyte is actually in the process of phagocytosing the homogeneous mass on the right. Unfortunately these features are not so prominent in the photographs as they appear by contrast when the stained and coloured smear is viewed under the microscope.

Klemperer *et alii* (1950) noted in post-mortem material peculiar nuclear alterations, with swelling, loss of chromatin structure and homogenization, occurring in mesenchymal cells of patients who died of disseminated *lupus erythematosus*. This material was found to contain large quantities of desoxyribose nucleic acid in a depolymerized state. The work of Lee *et alii* (1951) has shown, by means of Fuelgen and methyl green stains, that the inclusion bodies of L.E. cells also contain desoxyribose nucleic acid, and further, by their optical densities, that a considerable proportion of it is in a depolymerized state.

By the demonstration of L.E. cells in clotted blood it has been shown that no anticoagulant is necessary for their production and that, in the presence of active L.E. plasma, time outside the body is the limiting factor.

Holman (1951) drew attention to the fact that it has never been established that the nuclear degeneration and L.E. cell production occur *in vivo* and that their relationship to the hæmatoxylin-staining bodies found in various organs and to the pathogenesis of disseminated lupus must for the moment remain speculative. In view of the fact that these organs have been removed from the body or have died with the body, it would be interesting to examine for L.E. cells smears made directly from the bone marrow and blood of patients immediately and at intervals after death from disseminated *lupus erythematosus*. The opportunity to carry out this procedure has not arisen in Adelaide.

Another very simple technique for the demonstration of L.E. cells was described by Mathis (1951). Here again the patient's own blood is used. It is withdrawn into heparin and allowed to settle for thirty minutes. The buffy layer with the supernatant plasma is then transferred to a sterile centrifuge tube, incubated at 37° C. for forty-five minutes and centrifuged at 1500 to 2000 revolutions per minute. Smears are prepared from the buffy coat, and consistently positive results are claimed in disseminated *lupus erythematosus*. L.E. cells were recently demonstrated by this method in the blood of the patient whose case is reported in this paper.

Haserick (1951) is in agreement with Lee *et alii* (1951) in stressing that the specificity of the L.E. test is much greater than was previously accepted. The atypical symptoms of acute disseminated *lupus erythematosus* suggest that this disease may be much more widespread than is at present suspected, as evidenced by its presenting as premenstrual epileptiform attacks. A diagnostic search for L.E. cells is particularly recommended by Haserick when these attacks are present. Lee found in his series that the L.E. test had a sensitivity and specificity each of about 96%.

Since Haserick, Lewis and Bortz (1950) demonstrated that a γ globulin was the specific plasma fraction responsible for the phenomena induced by L.E. plasma or serum, a specific antibody has been produced in rabbits against the L.E. factor by the use of L.E. γ globulin as an antigen (Haserick and Lewis, 1950). This antiserum will precipitate the L.E. factor from plasma. More recently an agglutination test has been developed by Schleicker (1951) whereby washed group O IV Rh-positive red blood cells, when mixed with previously refrigerated egg albumin, are agglutinated by L.E. plasma or serum. Although the sensitivity of these tests is not fully known, it is possible that the usual methods of demonstrating the L.E. cell as a diagnostic procedure may soon become obsolete.

Summary.

A case of acute disseminated *lupus erythematosus* is presented.

A simple technique for the demonstration of L.E. cells, originally described by S. L. Lee, is recorded. L.E. cells were found with this method after the disease had undergone a remission. Various other techniques failed to reveal L.E. cells.

A photomicrograph is included which demonstrates the mode of production of L.E. cells.

The relevant and more recent literature is reviewed.

Acknowledgements.

I wish to thank Dr. F. Ray Hone for his consent to a thorough search for L.E. cells and for his permission to publish this case. My thanks are also due to Mr. Bonython Fuller for the photomicrographs.

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Reports of Cases.

A CASE OF HIRSCHSPRUNG'S DISEASE.

By RICHARD FLYNN,
Sydney.

P.W., a male patient, aged nineteen years, consulted me on January, 4, 1950. He complained of severe pain in his abdomen and had with him a radiograph of his large bowel after a barium enema, which showed megacolon. He stated that the condition had been diagnosed when he was six months old and that the pain had been relieved by poultices and high bowel lavages. He, or rather his mother, had learnt that to keep him from pain she had to see that he had an enema daily. This sometimes resulted in a good bowel movement, sometimes not, but it kept him well. However, it was a tedious process and they sought relief.

On January 14, 1950, with the patient under spinal anæsthesia reinforced by "Pentothal" administered by Dr. N. W. Bartrop, I divided his lumbar splanchic nerves on both sides and carried out an obstructive resection of his sigmoid colon, along with appendicectomy. His convalescence was uneventful, and once the clamp sloughed off the bowel his colostomy moved itself daily. The spur between the two loops was crushed and he was dismissed from hospital to return in April for closure of his colostomy opening. On April 29, 1950, his colostomy opening was closed, and on May 2 his bowels moved naturally. He still had a small fistula on June 8, but I felt that it would close of itself. I asked him to return in September. On September 1, 1950, he returned with the colostomy opening closed and his wound soundly healed, and he stated that his bowels moved naturally twice a week. A barium enema was given on September 5 and radiological examination made. Dr. A. F. Oxenham reported as follows:

> The barium enema flows freely through the large bowel back to the caecum. The ampulla of the rectum is regular and considerably dilated. There is fairly marked dilatation of all the colon. I have not the previous films for comparison. The bulk of the enema has been evacuated and the post evacuation film shows that the bowel has contracted to almost normal proportions.

Reviews.

MODERN HEADACHE THERAPY.

"MODERN HEADACHE THERAPY", by Friedman, is appearing for the first time.[1] It is designed to present to the general practitioner principles which will achieve the best results in caring for patients with chronic headache. The substance of the book is entirely the result of personal experience with over five thousand patients treated in private and hospital practice. Dr. Friedman has made a special study of headache from both diagnostic and therapeutic points of view, and the reader consequently realizes that this is no repetition of traditional statements from classical text-books.

The book is written in two main sections. The first three chapters deal respectively with diagnosis, treatment, and mechanism in general terms. The remaining six chapters describe in greater detail headaches due to intracranial, extracranial, and systemic disorders, migraine, and psychogenic and post-traumatic factors.

After reading the book, which can be done as a novel, one is reminded again of the fact common to all medical problems that if an adequate history is taken, and the patient thoroughly examined, an accurate diagnosis can be made and rational treatment instituted in most cases. Only in the minority of cases is ancillary investigation needed. This lesson is particularly valuable with a symptom like headache which tends to be as "distressing" to the doctor as to the patient.

The only criticism is that the book is written by one whose primary interest is the symptom of headache. We are already accustomed to those whose main interest is one system, or rarely one disease; but it seems a new departure to have a specialist in one symptom. And when one peruses the "Headache Chart" used for his history taking, examination and diagnosis in a "Headache Clinic", one feels that here is the real specialist who knows more and more about less and less. We feel that before being submitted to this type of investigation, a patient with a headache would be best "vetted" by a general practitioner or general physician. However, we congratulate Dr. Friedman on an excellent concise book which every general practitioner and physician would be wise to read or acquire. We would not recommend it as a book suitable for undergraduates.

CLINICAL PRACTICE IN INFECTIOUS DISEASES.

"CLINICAL PRACTICE IN INFECTIOUS DISEASES", by E. H. R. Harries and M. Mitman, has now been issued in a fourth edition.[2] For this edition the original authors have had the assistance of Dr. Ian Taylor. It can be readily understood why such assistance was necessary. The immense amount of work involved in revision and additions to such a text-book will be appreciated by all teachers in this field of medicine who endeavour to keep their lectures to students up to date.

An Australian reviewer of a previous edition stated: "Little or nothing in recent relevant literature has escaped them." Naturally the task of keeping abreast of modern research and treatment becomes more difficult year by year; yet, it is rather satisfying to note that large sections of previous editions have been able to be retained with little or no change in the text. One may be pardoned for attributing this to the clinical experience and acumen of the senior author and the careful selection of available material before insertion in previous editions.

Several changes, however, have been made in the arrangement of the various chapters. Under the new title "Rickettsial Diseases" there is a description of "Q" fever written by Dr. E. H. Derrick, of Brisbane, Deputy Director of the Queensland Institute of Medical Research. Naturally other references to Australian research workers and clinicians are made.

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[1] "Modern Headache Therapy", by Arnold P. Friedman, M.D.; 1951. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 9" × 5½", pp. 164. Price: 42s.

[2] "Clinical Practice in Infectious Diseases: For Students, Practitioners and Medical Officers", by E. H. R. Harries, M.D. (London), F.R.C.P., and M. Mitman, M.D. (London), F.R.C.P., with the collaboration of Ian Taylor, M.D. (London), M.R.C.P.; Fourth Edition; 1951. Edinburgh: E. and S. Livingstone, Limited. 9" × 6", pp. 728, with 20 plates and 48 text figures. Price: 30s.

This edition contains more illustrations in colour and half-tone than its predecessors. Many of these are excellent, but one might doubt the necessity to devote two whole pages to two rather poorly coloured plates—one of *Streptococcus pyogenes* and one of *Staphylococcus aureus*.

In a book of such a comprehensive nature as this it is easy to be critical of certain omissions, the importance of such omissions varying in degree according to personal opinions. For example, in the section on laryngeal diphtheria some might prefer a more detailed account of the bacteriology of the acute obstructive laryngitides. The condition laryngo-tracheo-bronchitis receives only a small footnote in which it is described as being probably of virus origin. Again in this section it is a little disappointing to find no reference to the organism *Hæmophilus influenzæ*, a not uncommon cause of acute obstructive "epiglottitis" and laryngitis in this country. In the chapter on poliomyelitis many will disagree with the dogmatic statement that the patient must be put into the respirator as soon as respiratory paralysis is suspected.

In its present form the title of this book is rather too modest and might be even misleading. As stated in Chapter 1, the term "infectious diseases" is limited in practice to those which are readily transmissible, the term "infective" being used for all diseases due to living agents. This book now covers a wider field than the so-called common infectious diseases. It is a book that contains much of interest to all physicians and research workers.

AN ATLAS OF RADIOGRAPHIC ANATOMY.

A BOOK entitled "An Atlas of Normal Radiographic Anatomy", edited by Isadore Meschan (assisted by R. M. F. Farrer-Meschan, of Melbourne), has been received from the publishers, W. B. Saunders Company, of Philadelphia and London.[1]

The work should be of particular interest to students of radiology and radiography. Many works have been published on radiographic positioning to obtain films capable of interpretation, but in all these the anatomical section has been most sketchy. The present work covers basic morbid anatomy as applied to radiography, the routine projection of anatomical structures and the resultant film. Changes during development and some of the more common variations from the normal are also dealt with. A short description of radiographic apparatus and methods is given in a preliminary chapter.

The illustrations are of good quality and line drawings of skiagrams of the various regions are helpful.

The technique of bronchography is most useful. Angiocardiography is described in a precise manner and the illustrations in this section are very good.

Much thought and time have been devoted to the compilation of this book; however, it should be of greater help to the student than to the established radiologist.

THE INTERNATIONAL PHARMACOPŒIA.

THE need for the establishment of international standards for all commonly used drugs was first expressed at the beginning of this century, and the publication of the first volume of the "Pharmacopœa Internationalis" by the World Health Organization brings this desirable objective nearer.[2] It also represents one positive step by the World Health Organization towards implementing its first objective—the attainment by all peoples of the highest possible level of health.

The committee responsible for publication (under the chairmanship of Dr. C. H. Hampshire, who was until recently secretary of the British Pharmacopœia Commission) has attempted to produce a common pool of drugs described in most national pharmacopœias, and also to produce a volume which may be used perhaps with local supplements, for those countries which at present have no pharmacopœia.

The standards laid down are reasonable and are in general somewhat at the same level as those specified in the British Pharmacopœia and the United States Pharmacopœia. In fact, as might be expected, many of the appendices and general notices are taken directly from the British Pharmacopœia or the United States Pharmacopœia. Thus we find that the definition of percentage solutions follows the British Pharmacopœia, a fact which may ultimately help to avoid confusion in the literature. One could have hoped for the wider use of more modern analytical techniques, but a more ambitious volume would have been required.

The principal name of each drug appears in Latin (unlike the United States Pharmacopœia and the next edition of the British Pharmacopœia) and many of the names used are not familiar to British medicine, for example, *Oleum Jecoris Aselli* for cod liver oil, *Secale Cornutum* for ergot. Most of the sulphonamides are included, but the description of antibiotics and "certain newer drugs" is reserved for Volume II. It is surprising that both insulin and thyroid are omitted from this volume, especially as the arrangement of the monographs would not lead one to expect these drugs to appear in Volume II. Lanatoside C, the important "original" glycoside present in *Digitalis lanata*, and from which digoxin is derived, is described, a fact which should help to make this substance more readily available. There are very few tinctures (paregoric is one of the survivors) and no ointments. Injections are to appear in Volume II, in which we should also like to see an attempt to produce international agreement on sterilization techniques for thermolabile drugs and possibly dressings and instruments.

Included in the appendices is a list of doses, both maximal and usual doses. As might be expected, some discrepancies are to be found—thus the "Pharmacopœa Internationalis" maximal single dose for mercuric chloride is 15·0 milligrammes whilst the British Pharmacopœia gives 4·0 milligrammes; for phenobarbitone it gives 300 milligrammes contrasted with the British Pharmacopœia 120 milligrammes, and the doses of all liquids are given in grammes, not in units of volume. If larger doses than the maximal are prescribed, the physician must indicate his wishes in some way on the prescription, and the prescription is not to be repeated by the pharmacist, who shall refuse to supply doses larger than the maximal without these explicit instructions.

The "International Pharmacopœia" has no legal standing in British countries where, of course, the British Pharmacopœia standards are required to be observed. The future of the "Pharmacopœa Internationalis" as far as Australia is concerned will no doubt be confined to its influence on further editions of the British Pharmacopœia, or perhaps ultimately as a basis of standards for an Australian pharmacopœia.

MENSTRUAL DISORDERS AND STERILITY.

THE third edition of "The Diagnosis and Treatment of Menstrual Disorders and Sterility", by Charles Mazer and S. Leon Israel, is a complete revision bringing this excellent book right up to date.[1] The title is possibly misleading, as it might be construed to mean the role of menstrual disorders in the treatment of sterility, instead of which the book really covers menstrual abnormalities (amenorrhœa, dysmenorrhœa and uterine bleeding) in the first portion and the diagnosis and treatment of sterility in the latter half.

Perhaps the main reaction on picking up this volume is the pleasure given by the quality of its paper and layout. The photomicrographs are of high standard. The chapters are short and make reference easy for any particular symptom. The book is essentially easy to read and its clinical approach is one of its main values. If criticism were to be offered, possibly the subject has been over-simplified, although at the end of each chapter is a full bibliography for those who wish to delve more deeply. The latest trends of modern gynæcology are dealt with—especially in chapters dealing with intraepithelial carcinoma of the cervix, vaginal smear technique of Papanicolaou, and the medical treatment of endometriosis.

The authors are very optimistic throughout the book about endocrine therapy. While the endocrines are undoubtedly of benefit in a few selected cases, their use and abuse by general practitioners are all too widspread already.

[1] "An Atlas of Normal Radiographic Anatomy", by Isadore Meschan, M.A., M.D., with the assistance of R. M. F. Farrer-Meschan, M.B., B.S.; 1951. Philadelphia: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 10½" × 7", pp. 602, with 1044 illustrations. Price: £7 2s. 6d.

[2] "International Pharmacopœia"; First Edition; Volume I; 1951. Geneva: World Health Organization. 9½" × 6½", pp. 424. Price: 35s.

[1] "Diagnosis and Treatment of Menstrual Disorders and Sterility", by Charles Mazer, M.D., F.A.C.S., and C. Leon Israel, M.D., F.A.C.S.; Third Edition; 1951. New York: Paul B. Hoeber, Incorporated. 9½" × 6½", pp. 598, with 137 illustrations. Price: $10.00.

Amenorrhœa is dealt with very completely in chapters analysing its causation by pituitary, ovaries and uterus. The latest methods of treatment include the use of cortisone and ACTH in derangements of the adrenal glands, and low dosage irradiation in amenorrhœa is discussed in detail. The chapter on dysmenorrhœa is very full and the treatment is mainly conservative. However, the use of a stem pessary is not favoured nearly so much by gynæcologists in this country; and the advice that "if there is another indication for a lower abdominal section in a woman subject to dysmenorrhœa, resection of the pre-sacral nerve should be simultaneously performed" (page 149) is surely too radical.

The chapter on premenstrual tension is particularly useful. This problem recurs very frequently in practice and is not well dealt with in most gynæcological text-books.

One cannot agree with everything in the book. Surely it is dangerous to advise emptying the uterus surgically in cases of missed abortion because of the emotional reactions of a patient or her friends to the carrying of a dead fœtus. The injection of progestin in threatened miscarriage is losing supporters in Australia and much more faith is placed in large dosage stilbœstrol therapy. Then again we must join issue with the widespread recommendation of Cæsarean section at approximately the thirty-seventh week in toxæmia or its use to terminate the pregnancy of an Rh-negative patient with antiagglutinins. World figures undoubtedly show the fœtal survival rate in Rh affections to be much better when the pregnancy is terminated by means other than Cæsarean section. Routine diagnostic curettage is advised to be carried out in the consulting room. We cannot agree that this is advisable or safe—as distinct, of course, from an endometrial biopsy.

In these days of endocrine therapy, orally as well as by the magical injection, a very useful table is provided in Chapter II, showing the relative potency of available œstrogen preparations.

The latter half of the book covers the investigation of sterility, or, as the authors prefer, "barren marriages", fully and ably from both male and female angles. Male subfertility is an often neglected aspect of sterility and this is excellently summarized by a logical approach to treatment through diagnosis.

In spite of some disagreement with the authors of this book, it is recommended for a place in the reference shelves of any who engage in gynæcological practice.

TREATMENT BY MANIPULATION.

THE small, concise volume by Burrows and Coltart on "Treatment by Manipulation" is a valuable guide, giving the rationale, the art and indications for a surgical procedure long neglected by many of the medical profession.[1] It will be a counter to the practice of regarding the "unqualified" as the only experts in manipulative treatment.

As stated, the immediate object of manipulation is to move a joint through its full range, but is it not possible that movement beyond that full range is sometimes necessary? Warnings are given and reasons for failure are stressed—for example, ignorance of the right type of case, failure to apply the right technique, and neglect of after care. Manipulation can become an art requiring often very little but a properly applied force with correct timing, for which anæsthesia may not always be necessary. The authors, however, prefer to use anæsthesia. Full details, with good illustrations in the second half of the book, give valuable help in an easily assimilated way for the many affections of individual parts.

The use of a Sayre's or Glisson's sling for distraction in the manipulation of the cervical part of the spine has been omitted, but it is extensively used with satisfactory results.

A discussion of the importance of the intervertebral disk and the zygopophyseal joints in the lumbar region would have been welcomed. According to some authorities, the disk is the most important single factor in the ætiology of low-back pain and sciatica. The initial paragraphs devoted to terminology clarify many vague definitions; however, it is difficult to avoid using the term periarthritis in the shoulder where adhesions are the only factor. In all its 36 pages the reader is presented with a digest well worth while, and no practitioner should miss reading this book, if only to be able to guide the patient along orthodox channels.

[1] "Treatment by Manipulation", by H. Jackson Burrows, M.D., F.R.C.S., F.R.A.C.S., and W. D. Coltart, M.B., F.R.C.S.; Second Edition; 1951. London: Eyre and Spottiswoode. 8½" × 6", pp. 80, with 29 illustrations. Price: 12s. 6d.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Textbook of Surgical Treatment: Including Operative Surgery", edited by C. F. W. Illingworth, C.B.E., M.D., Ch.M., F.R.C.S.E., F.R.F.P.S. (Glasgow); Fourth Edition; 1952. Edinburgh and London: E. and S. Livingstone, Limited. 10" × 6½", pp. 756, with 381 illustrations. Price: 45s.

Intended mainly for senior students and those undergoing training in surgery.

"Textbook of Gynæcology", by Wilfred Shaw, M.A., M.D. (Cantab.), F.R.C.S. (England), F.R.C.O.G.; Sixth Edition; 1952. London: J. and A. Churchill, Limited. 9" × 6", pp. 680, with four plates in colour and 304 text figures. Price: 27s. 6d.

The fifth edition was published in 1948.

"The Queen Charlotte's Text-Book of Obstetrics", by the following members of the Clinical Staff of the Hospital: G. F. Gibberd, M.B., M.S., F.R.C.S., F.R.C.O.G., Arthur C. H. Bell, M.B., B.S., F.R.C.S., F.R.C.O.G., Hon. M.M.S.A., Douglas Macleod, M.S., F.R.C.P., F.R.C.S., F.R.C.O.G., W. R. Winterton, M.B., F.R.C.S., F.R.C.O.G., H. G. E. Arthure, M.D., F.R.C.S., F.R.C.O.G., Briant Evans, M.B., B.Ch., F.R.C.S., M.R.C.O.G., Kathleen M. Robinson, M.D., F.R.C.S., M.R.C.O.G., S. G. Clayton, M.D., M.S., F.R.C.S., F.R.C.O.G., with the assistance of Thomas Hunt, D.M., F.R.C.P., A. White Franklin, M.B., B.Ch., F.R.C.P., E. Rohan Williams, M.D., F.R.C.P., F.F.R., D.M.R.E., J. Murray, M.D., G. W. B. James, C.B.E., M.C., M.D., D.P.M.; Eighth Edition; 1952. London: J. and A. Churchill, Limited. 9½" × 6½", pp. 544, with four coloured plates and 273 text figures. Price: 37s. 6d.

The first edition appeared in 1927, the seventh in 1948; the present edition has been "thoroughly revised".

"Manual of Leprosy", by Ernest Muir, C.M.G., C.I.E., M.D., F.R.C.S. (Edinburgh); 1952. Supplement to the first edition. Edinburgh and London: E. and S. Livingstone, Limited. 8½" × 5½", pp. 16. Price: 2s. 6d.

Deals with sulphone treatment.

"Bacteria", by K. A. Bisset, D.Sc., assisted by F. W. Moore, B.Sc.; 1952. Edinburgh and London: E. and S. Livingstone, Limited. 10" × 7", pp. 132, with 38 illustrations. Price: 20s.

An attempt "to correlate the description of such morphological, biochemical, and ecological characters of bacteria as are regular in occurrence and of systematic value".

"Causes and Prevention of Tuberculosis", by Brice R. Clarke, M.D., with a chapter on mass miniature radiography by Joseph Ritchie, L.R.C.P., L.R.C.S., and a foreword by Professor J. H. Biggart, C.B.E., M.D., D.Sc.; 1952. Edinburgh and London: E. and S. Livingstone, Limited. 10" × 7", pp. 296, with 13 text figures. Price: 32s. 6d.

The author has tried to give a complete picture of the method of infection, social and environmental factors and the influence of food, of age, of race and of family.

"Diseases of the Nose, Throat and Ear: A Handbook for Students and Practitioners", by I. Simpson Hall, M.B., Ch.B., F.R.C.P.E., F.R.C.S.E.; Fifth Edition; 1952. Edinburgh and London: E. and S. Livingstone, Limited. 7½" × 5½", pp. 476, with 82 illustrations, eight in colour. Price: 18s.

The first edition was published in 1937.

"Ear, Nose and Throat Diseases: For the General Practitioner", by William McKenzie, M.B., B.Chir. (Cantab.), F.R.C.S. (England); 1952. Edinburgh and London: E. and S. Livingstone, Limited. 7½" × 5", pp. 144, with two plates and eight text figures. Price: 9s.

"Not a text book, but simply an account of my specialty written to interest the doctor in general practice."

"Introduction to Clinical Neurology", by Gordon Holmes, M.D., F.R.S.; Second Edition; 1952. Edinburgh and London: E. and S. Livingstone, Limited. 10" × 6½", pp. 196, with 43 text figures. Price: 12s. 6d.

The first edition was published in 1946.

The Medical Journal of Australia

SATURDAY, MAY 17, 1952.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: surname of author, initials of author, year, full title of article, name of journal without abbreviation, volume, number of first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

WORDS.

On November 15, 1951, when Lady Violet Bonham Carter delivered before the Royal College of Physicians of London the Lloyd-Roberts Lecture on "The Power of Words", she gave that august and erudite body much food for thought and, we should imagine, a great deal of pleasure. Most of what she said has been set like a choice repast before the medical profession at large.[1] She started by saying that she had always loved words, and all who are like her in this will read her lecture with pleasure. She said that she loved them for their beauty and their strange power and she added that "they can make a blank sheet of paper glow with all the colours of a Turner sky . . . they can fill the air with music in a silent room. They are, as Mr. Ivor Brown says, the blossom of thought; yet they may also be the seed of action. They can act on men like dynamite, stirring them to tremendous deeds. They can lull them to sleep like poppy or mandragora. They can lead and they can mislead. They can put truth on a candlestick or hide its light". Lady Carter divided her lecture into three main sections, dealing in turn with public speaking, broadcasting and the written word. Few members of the medical profession have to engage in broadcasting, but the same cannot be said of public speaking or writing. Those who take any part in the corporate life of the profession must be prepared to present to their fellows their views on scientific or medico-political matters and to discuss what others have said. This may all be included under the heading of public speaking. In the same way most medical graduates find at some time or other that they have to set out their views on paper. Everyone will agree that the effectiveness of such statements, spoken or written, will depend largely on the words chosen for them. Let us then confine our attention at the moment to spoken and written words.

Every reader of this journal will be able to recall speakers who have held his attention by what they have said and by how they have said it. In the world of medicine such speakers are all too rare. They may be able, as Gladstone said of oratory (this is quoted by Lady Carter), "to draw emotion from an audience like a mist—and to pour it back in a flood"; on the other hand the intellectual content and the ordered sequence of the stages of argument are potent factors. Every reader has, in contradistinction, suffered in silence with "groanings that cannot be uttered" from the dull, flat and inconsequential outpourings of earnest but misguided souls seeking to do their duty. Lady Carter quotes Mr. Winston Churchill's advice about speaking: "What matters first and most is *who* you are. What matters next is *how* you say it. What matters last and least is *what* you say." This is no doubt an overstatement and Mr. Churchill would probably be the first to admit it. What is undoubtedly true is that what you say may be made doubly effective by how you say it. When a visitor from another State or another country with some kind of reputation (not necessarily for ability to speak) is billed to talk to a medical audience, those who attend come prepared to approve of the speaker and his speech—their minds are like soil carefully prepared in which the sower may sow his seed. When a medical man speaks among his everyday associates, it is often only "old So-and-So", and he is unfortunate because he has to rely on how he talks and what he says. Lady Carter thinks that there are very few "golden rules" in public speaking, but she recalls some which she uses herself.

First try at the very outset of your speech to betray yourself somehow to your audience. Get on to personal terms with them, and they will forgive you—perhaps not everything—but at least a good deal.

Next, make them feel that your speech is not a recital or a performance but a cooperative business, a partnership in which they are playing an important part; that they are influencing it all the time; and that if you were speaking to any other audience in the world it would be a different and probably a very inferior speech.

The "how to say it" is most important to a medical speaker. This does not necessarily mean that every doctor should be trained in elocution. Medical teachers and others who have to do much speaking will be well advised to study the art; others should try to remember to speak distinctly and at least to use grammatical phrases and sentences. It is unfair to expect any audience to do translation while listening to a speech. One important point arises here. Thoughts are said to be clothed in words and we must admit that different occasions may call for different kinds of clothing. A formal occasion demands that thoughts shall be in formal dress; an informal occasion, such as a discussion at the bedside or in the laboratory, may allow to thoughts some laxity in apparel. The clothing, however, must never be slovenly. In this respect the clothing of thoughts is like the cultivation of good manners. There is never a sound excuse for the display of bad manners. So with thoughts and words.

Turning to the written word, we note that Lady Carter refers first of all to books that have made history and then to the fact that few of us can live without books. Books indeed may play an important part in therapeutics. This was discussed in these columns some years ago in an article entitled "The Therapeutic Value of Reading". Books, Lady Carter reminds us, are as necessary to most of us as food, as sleep, as the air we breathe. "To travel without a book would be as unprovident as not to pack a toothbrush. . . . To sleep without a book beside one's bed . . . would be almost as difficult and as uncomfortable as

[1] *The Lancet*, December 1, 1951.

to sleep without a pillow under one's head." We all have our favourite books and most of us can recall from them passages which we love. Many readers of this journal will recall with pleasure Professor J. Burton Cleland's "Acceptable Words" which he recorded some years ago in this journal. A great deal might be written about words of this kind, but we must return to the medical practitioner's use of words. He has to write words as well as speak them. Sometimes he speaks his written words later on to an audience—it would generally be better if he did not read them but remembered them. When he writes words for others to read he has to take care—no word can really replace *le mot juste*, even in medical reports and other scientific contributions. The temptation to dilate on this aspect is hard to resist; it may perhaps be partly satisfied by the recommendation to study such books as A. P. Herbert's "What a Word" and T. H. Savory's recently published "Browsing Among Words of Science".

A final point remains. We all recognize the tremendous power of words. While we know, as Solomon tells us, that "a word fitly spoken is like apples of gold in pictures of silver", we need to remember that there are occasions, by no means few in number, when words are better left unspoken. William Hazlitt wrote that words are the only things that last forever—even spoken words cannot be unsaid. Let us therefore be certain that our words are true, that it is wise to speak or to write them, that they are kind and are not intended to glorify ourselves and that they do not unwittingly proclaim our intellectual myopia. If words have to be used to correct an abuse or to curb iniquity, in other words if this use is wise, then let them be clear, forthright and unmistakable. We should always know what we are doing.

Current Comment.

OVERCROWDING IN MENTAL HOSPITALS IN SOUTH AUSTRALIA.

SOME important facts are stated in the thirty-seventh report of the Director-General of Medical Services of South Australia on the Parkside Mental Hospital, Northfield Mental Hospital and the Enfield Receiving House for the year ended June 30, 1951. The total number of patients on the register of mental institutions in South Australia on June 30, 1951, was 2557. This represents a ratio of 3·35 mental patients per 1000 of the population. The highest ratio for Australia is in New South Wales, 3·79; the lowest is in Western Australia, 2·61. Dr. H. M. Birch, the Superintendent of Mental Institutions, discusses the increases in the number of patients. (He makes his report to the Director-General of Medical Services.) He points out that at the end of the year the number of patients actually in residence showed the following variation: the number at Parkside increased by 31, Northfield had a decrease of five, and the Enfield Receiving House had three more, making a net increase of 29 for the three institutions. In the previous year the overall increase was 99 persons. Dr. Birch points out "again" that the mental institutions are so overcrowded that corridors and day rooms have had to be used for sleeping quarters, and that at the present time there exists approval for new buildings which will accommodate only 50 patients. The proposed new buildings at Northfield Mental Hospital for 260 senile patients and mentally deficient children are still in the hands of the architect. Referring to the planning for the next ten years, Dr. Birch calls attention to the increase of the State's population of 58,945 persons during the past three years. This, he states, represents an annual increase of approximately 3%, and as the ratio of patients in mental hospitals is 3·31 per 1000 of population, the increase in the mental hospitals on a population basis alone is calculated to be some 65 persons every year. This means that the official planning for mental hospitals is so arranged that the overcrowding will increase. These facts should be made as widely known as possible in South Australia.

THE INDICATIONS FOR SPLENECTOMY.

INTEREST in the indications for removal of the spleen is perennial, as knowledge of this somewhat mysterious organ grows, and as hæmatologists learn to interpret in more and more precise detail the changes in the blood and in the other blood-forming organs, which are due to or accompany the disorders of the spleen. The subject was considered at a meeting of the New South Wales Branch of the British Medical Association in July, 1950, when papers were read by C. R. B. Blackburn and W. L. Calov, and an informative discussion followed.[1] On this occasion the viewpoint presented was particularly that of the physician, and it is interesting to turn to a surgeon's treatment of the subject in a paper presented by Rodney Maingot.[2] The indications for splenectomy are placed by Maingot into two groups: conditions in which splenectomy is indicated, and conditions in which splenectomy may be indicated. Splenectomy is regarded as being indicated as an adjunct to other surgery in various circumstances which we need not list here, and in cases of ptosis of the spleen or wandering spleen, rupture of the spleen, congenital hæmolytic anæmia, idiopathic or primary *purpura hæmorrhagica*, idiopathic or primary splenic neutropenia, idiopathic or primary panhæmocytopenia, cysts of the spleen (parasitic or non-parasitic), and primary tumours such as lymphosarcoma. Conditions listed in which splenectomy may be indicated are congestive splenomegaly (portal hypertension), acquired hæmolytic anæmia, secondary *purpura hæmorrhagica*, secondary panhæmocytopenia, lymphoblastoma, Boeck's sarcoid, tuberculosis of the spleen, "Egyptian" splenomegaly (schistosomiasis), Gaucher's disease, and splenomegaly of unknown origin. Maingot goes on to discuss these various conditions in some detail, and offers suggestions on the technique of splenectomy. An important point during operation to which he draws attention is the need to search for accessory spleens, which, he states, should always be removed whenever they are found. In certain conditions an overlooked accessory spleen may grow in stature and reproduce the disease—for example, idiopathic purpura—for which the primary splenectomy was undertaken. In certain of the conditions listed, in which splenectomy is regarded as indicated, a low operative mortality is combined with excellent late results. Such conditions are ptosis, primary purpura, congenital hæmolytic anæmia, primary splenic neutropenia, idiopathic panhæmocytopenia, and cysts of the spleen. In cases of hypersplenism and those forms of cytopenia due to a variety of known causes, the operative mortality is low, but the late results are disappointing. Of conditions in the second group, those in which splenectomy may be indicated, Maingot regards the most frequent and hopeful indications as congestive splenomegaly and acquired hæmolytic anæmia. The terms "congestive splenomegaly" and "portal hypertension" are used nowadays to cover older terms such as "splenic anæmia", "Banti's disease" and "Banti's syndrome". Experience of operative intervention in this condition or group of conditions is growing, but it still has many pitfalls. Maingot states that in most cases of portal hypertension splenectomy should be combined with spleno-renal or porto-caval anastomosis. The operative mortality remains high, and this he regards as being in part due to

[1] THE MEDICAL JOURNAL OF AUSTRALIA, October 28, 1950.
[2] *The Lancet*, March 29, 1952.

the nature of the disease, faulty selection of cases and imperfections in the technique of vascular surgery. In the hands of the experienced surgeon who has made a special study of portal tension, the results in selected cases are described as promising. In the other conditions included in the second group, Maingot lists the following principal reasons for advocating surgery: to rid the patient of the encumbrance occasioned by the presence of a large, weighty and friable spleen; to mitigate or arrest, for an unknown period, the evil effects of hypersplenism; to forestall rupture of the organ; to excise an enlarged spleen of obscure ætiology, in the hope that some cryptic process may be controlled.

This neat list of indications for splenectomy offered by Maingot helps to clarify our thinking on the subject, although it needs to be used in the light of the more detailed comments in his paper. On the other hand, there are other ways of looking at the problem, and it is helpful to refer to certain broader principles suggested by Calov in the paper mentioned earlier. It was stated there that the problem of splenectomy in any particular case might be tackled by posing and answering the following questions: Is hypersplenism present? Is hypersplenism incidental in the course of the illness, or is it the prime factor? If it is incidental: (i) is the patient able to stand splenectomy, and if so, (ii) will the benefits of splenectomy be such as to improve the patient's chances of recovery or materially influence the progress of the disease? Calov pointed out that if hypersplenism appeared to be the main factor in the illness, the important thing was the exercise of judgement as to blood transfusion and the selection of a time for the operation. He then added two further questions in relation to hæmolytic anæmia: If hæmolytic anæmia is present, is it familial or acquired? If it is familial, is there evidence of spherocytosis and of the other characteristics of familial acholuric jaundice? He considered that if the answer to these questions was "yes", then splenectomy at the proper time was the correct treatment. In cases of acquired hæmolytic anæmia, although splenectomy was not likely to be of value, he believed that it sometimes effected considerable improvement and might be curative. No doubt the remaining problems on the subject will eventually be solved as the physician, the surgeon and the hæmatologist work together.

THE REVERSIBILITY OF RHEUMATIC AND OTHER CONDITIONS.

THE flood of literature dealing with cortisone and ACTH has already exceeded the ability of any single person to sound it with critical comprehension. There are, however, aspects of the subject which are extremely important in relation to the modes of thought by which the important discoveries were made, and these are worth study by all those who earnestly wish to lift another corner of the veil which hides so much of the processes of life. Recently these pages contained a brief appreciation of Kendall's own modest account of the steps leading to the final stages of his synthetic studies. Equally interesting is Philip S. Hench's Nobel lecture delivered in Stockholm in December, 1950, and recently published.[1] Hench tells how he began his inquiries into rheumatic disease in an atmosphere of pessimism, but in 1929 a patient told him how he had been relieved of rheumatoid manifestations within a few days of the appearance of jaundice, and this started a train of thought which suggested that reversibility of these lesions might be within the reach of the therapist of the future. The patient in question was free of his troublesome arthritis until several weeks had elapsed after the onset of the jaundice. During the next few years the attention of many physicians was drawn to Hench's published accounts of similar observations; many of us pondered over this problem, but few were stimulated to action. The alleged irreversibility of the lesions of rheumatoid arthritis had been disproved, but it did not seem that jaundice, considered as a visual evidence of a biochemical change, was *per se* the ameliorating agent. Experiments proved that hyperbilirubinæmia alone did not bring about remissions, and "Nature's dramatic antidote" could be imitated only feebly, if at all. Therefore the hypothetical substance was other than bilirubin. The ameliorating effect of pregnancy was then well known, and gave rise to further speculation. During the decade following the original speculations about jaundice Hench and his colleagues felt stimulated rather by their failures to induce experimental remissions than by interrelating clinical observations to the general problem. At this stage they decided that rheumatoid arthritis was potentially reversible and that an anti-rheumatic "substance X" existed, made manifest by pregnancy and jaundice, but evidently not a unisexual hormone or a metabolic product of a disordered hepatic state. This substance they further thought was a chemical or biological entity normally present in the body, specific in both nature and function, and, in view of the existing evidence, probably a bisexual hormone. It will be seen that this logical approach was by no means an inspired guess, though the next step was perhaps more speculative. Hench took into his counsels Kendall, whose work has been already described in these pages, and it is certainly both interesting and curious that at this time Kendall and his associates were actually working on the identification and synthesis of a substance which was either Hench's "substance X" or a very close relation. Though the final links of the work relating the relief of rheumatoid arthritis to an untried adrenal hormone were at the time unsubstantial, and though the workers were often in great doubt whether they were pursuing an unreal vision, they did not confuse the apparently sound part of their doctrine with their empirical trials of various substances. The final idea which underlay the selection of Kendall's adrenal cortical substance was perhaps somewhat shadowy, but had some basis in fact. This was the observation that fatigue and low blood pressure were common accompaniments of rheumatoid conditions, which suggested the possible validity of the use of an adrenal hormone, even though no supporting information could be obtained from autopsy studies. Kendall's compound E increased resistance of animals against the reactions following administration of typhoid vaccine, and this and similar preparations were known to give remissions in a good proportion of cases of rheumatoid arthritis. Thus the use of Kendall's compound seemed to be justified, but the enthusiasm of Hench and his colleagues had to be kept alive for another eight years before a sufficient amount of the substance was available for clinical trial.

The rest of the story is well known; at last success was gained in the treatment of a woman badly crippled with rheumatoid arthritis in 1948, and early the next year the logical step was taken of using ACTH for the same purpose. From this point Hench's Nobel lecture pursues the present status of both these remarkable substances in general medicine, refers to the side effects, and candidly states the gaps in our knowledge. It may be noted in passing that we do not yet know the output of cortisone or ACTH in the human body, or the degree of stimulation of the adrenals by ACTH. Very little is known of the metabolic career of cortisone, and we are ignorant whether other similar hormones exist. After giving a brief but copiously documented account of the existing state of knowledge about the practical applications of these hormones, Hench sums up the position by saying that cortisone and ACTH today represent unframed pictures, but aptly quotes Starling's remark: "The physiology of today is the medicine of tomorrow." We may with equal aptness here return to our text, that this long and patient work has shown that disease processes thought to be irreversible have been proved otherwise, and it may yet be in our power to arrest or even reverse pathological changes which at present seem doomed to progress despite all that we can do. This hope lies unexpressed in the minds of men and can reach the light of day only by the help of those qualities which are not dimmed by a lifetime dedication or by repeated failures.

[1] *Annals of Internal Medicine*, January, 1952.

Abstracts from Medical Literature.

SURGERY.

The Surgical Treatment of Colloid Cyst of the Third Ventricle.

WYLIE MCKISSOCK (*Brain*, Volume LXXIV, Part I) reports on a series of 21 cases of surgical treatment of colloid cyst of the third ventricle encountered over the last eleven years. He states that in fifteen cases the patients are still living. He stresses the fact that it is of utmost importance to have a correct pre-operative diagnosis, otherwise the operation almost certainly leads to the death of the patient. Ventriculography is important in establishing the diagnosis. If the cyst cannot be removed he advocates its electrocoagulation. Recurrence is unusual.

Open versus Closed Method of Colon Anastomosis.

C. F. KITTLE, T. F. ORR, JUNIOR, AND T. F. ORR (*A.M.A. Archives of Surgery*, June, 1951) review the problem of colon anastomosis. They state that the evil results of early open anastomosis led to many attempts to overcome the dangers of peritonitis. Exteriorizing operations, obstructive resections of the Rankin type and aseptic methods were introduced. Ochoner and DeBakey in 1939 declared that primary resection of the colon with immediate anastomosis should never be done. In the years since then there has been a gradual swing of opinion towards the attitude that the method employed is adequate if the results are good. Various authorities and reports are quoted to emphasize the view that the mortality and morbidity are at least as low with the open methods as with the closed. The obvious advantages of more accurate suturing and of a more adequate stoma which the open method offers were felt to be crucial by the authors. They state that, regardless of the type of anastomosis used, peritonitis does not result so frequently from soiling at the time of operation as it does from subsequent leakage due to defects in technique. They regard primary one-stage resection and open anastomosis as safe for any portion of the colon without preliminary or complementary colostomy, unless obstruction exists or when perforation and infection at the site of the lesion make primary resection hazardous.

Extensive Resection of the Small Intestine.

J. H. JOHNSTON (*The Lancet*, April 19, 1952) describes extensive resection of the small bowel of a man, aged fifty-seven years, weighing seven stone one pound, who had had gastro-enterostomy performed twenty years previously for duodenal ulcer. For several years he had had periodical central abdominal pain coming on about two hours after the taking of food and relieved by vomiting. On admission to hospital he was in pain and had tenderness in the umbilical region but no rigidity. A provisional diagnosis of recurrent peptic ulceration was made. The symptoms subsided after a few days on a peptic ulcer regime, but some days later an urgent abdominal condition supervened and laparotomy was undertaken. The peritoneal cavity was found to contain foul blood-stained fluid, and gangrenous small intestine presented. A tight band of omentum was encircling the root of the mesentery and causing strangulation, the mesenteric veins being distended with blood clot. The entire small intestine, except two feet of jejunum just distal to the gastro-enterostomy stoma and the last three inches of ileum, was gangrenous. The omental band was divided, the gangrenous bowel was resected and an end-to-end anastomosis was made between the jejunum and the ileum. At the end of the operation there was about two feet of small intestine between the stomach and the caecum. The patient's condition improved after the resection. Four days after operation he was given a diet rich in protein, supplemented with vitamins. Twelve days after operation he weighed six stone nine pounds. Five weeks after operation he was on a full diet and four months after operation he weighed eight stone ten pounds. The author states that compensatory changes develop after extensive bowel resection; these include delay in gastric emptying with prolongation of gastric digestion. The patient has had few after-effects. He has been denied the compensation of delayed gastric emptying and the absorbing surface of the duodenum, but he has gained in weight. His chief complaint is that the call to defæcate comes suddenly and must be obeyed.

Potassium Deficiency in Surgery.

W. H. COLE (*A.M.A. Archives of Surgery*, June, 1951) discusses the significance of variations in the serum potassium level in surgical cases. He states that the sodium, potassium and chloride determinations are of significance only if they are lower than normal. Difficulty arises in knowing how much of these should be given to adjust the balance, and unfortunately before one knows that too much has been given one must wait for toxic manifestations—cardiac damage with positive electrocardiographic findings in the case of potassium, renal dysfunction, œdema *et cetera* with sodium and chloride. Potassium deficiency is commoner after operation than is usually recognized. In one series a figure below 3·2 milliequivalents per litre was found in 9 of 30 cases of operations on the biliary tract. After 38 consecutive major surgical procedures 26 patients had a lowered serum potassium level. The chief factors in this are lack of food intake, vomiting, gastro-intestinal decompression, urinary excretion, fistulæ and diarrhœa. It is of interest to recall that there is actually about twice as much potassium as sodium in the body, 98% of it being intracellular. Unlike sodium, the kidney will excrete potassium even if there is a deficiency. With dehydration the kidney preferentially secretes potassium in place of sodium. With starvation the loss of potassium may be great. Benedict showed long ago that 2·87 milliequivalents of potassium are lost with each gramme of protein. The chief post-operative loss is in the first twenty-four hours, partly because of the high nitrogen loss at this time. Adrenal cortical hormones also increase excretion. Alkalosis is frequently, though not always, present, and may be the cause of potassium deficiency. Potassium deficiency may determine the failure of alkalosis to respond to sodium chloride therapy. If alkalosis with a carbon dioxide volume above 60% persists in patients with vomiting after adequate hydration and saline therapy, then potassium deficiency must be suspected. The clinical manifestations are vague; the low amplitude of the *T* wave, the prolonged *Q-T* interval and the serum potassium estimations are the most dependable. Other effects are weakness, anorexia, drowsiness, apprehension and irrationality, and diffuse pains. The picture may vary widely. Potassium chloride is used in replacement therapy. Two to three grammes per day usually replace the daily loss. Doses up to six grammes will usually bring the potassium level to normal in a few days. In the presence of low levels of potassium and good renal function, as much as 12 to 15 grammes of potassium chloride can be given in as many hours. Up to six grammes of potassium chloride can be added to one litre of various infusion fluids, provided it is not added to fluids already hypertonic.

Colonic Replacement of the Stomach.

V. B. HARRISON (*The Lancet*, January 5, 1952) presents the early results of radiological investigation of 30 patients treated by colonic replacement of the stomach and followed for at least six months. He states that the results indicate that the technique is of value in the treatment of peptic ulceration and of early post-gastrectomy syndromes. A "stomach mechanism" is produced which has considerable capacity and shows movement, the colonic segment regurgitating the meal frequently into the stomach remnant and ensuring some degree of mixing and maceration of the food. Chyme enters the small bowel intermittently, and by the normal route. Thus the essential intimate contact between intestinal contents and intestinal mucosa is ensured. Passage through the small bowel may be rather slower than before operation. The meal normally reaches the ascending colon six hours after ingestion. The site of resection of the colonic segment is not identifiable after operation, but the level of the hepatic flexure is always lowered. The author states that although early results have been most encouraging, further clinical and physiological studies will be essential before the operation can be finally assessed.

The Perivascular Neural Pattern of the Femoral Region.

F. ROLAND WILDE (*The British Journal of Surgery*, September, 1951) states that the vascular nerves to the deep lower limb vessels may be rendered available for direct study by the application of a dissection technique, certain precautions being observed regarding the type of material used and the method of its fixation. Human fœtuses and the rhesus monkey show a number of femoral vascular nerves derived from the femoral nerve trunk and its immediate branches. These vascular nerves supply the whole of the common femoral and the superficial femoral vessels from the inguinal ligament to the hiatus in the *adductor magnus* muscle. The femoral nerve may well constitute the exclusive source of

innervation of these vessels, though no such formal conclusion is advanced on the basis of the present limited series of dissections. A coarse nerve plexus formed upon the main arterial and venous trunks is composed of longitudinal nerve strands intercommunicating at intervals by means of fine transverse filaments lying at right angles to the long axis of the vessels. This reticular formation is reinforced periodically by direct contributions from the principal local nerve trunks. In the human subject this adventitial plexus clothing the main axial femoral vessels is richly beset with Pacinian corpuscles. It is suggested therefore that functionally the plexus is largely sensory in nature and that it may constitute a component of the deep sensory pathways. Vascular (that is, perivascular) nerves are traceable from the main local nerve trunks (or their branches to muscles) to the secondary and tertiary branches of the deep (and predominantly "muscular") vessels, such as the medial and lateral circumflex femoral vessels. These nerves to "muscular" arteries are devoid of Pacinian corpuscles. They afford an anatomical basis for the neural control of deep "muscular" arteries.

Carcinoma of the Male Breast.

PHILIP SOMERVILLE (*The British Journal of Surgery*, January, 1952) reports 19 cases of carcinoma of the male breast and reviews the literature. The condition, although uncommon, occurs with sufficient frequency to warrant close attention. The ratio of male to female persons affected is about one in one hundred. The author describes the clinical and pathological findings in his case and also deals with the treatment and follow-up. Carcinoma may occur in the breast of males of any age group, but the average age for males is slightly higher than for females. In his review of ætiological factors, the author states that, although trauma is often mentioned in case histories, it remains of doubtful significance. There is good evidence to show that hormonal stimulation plays a large part in the ætiology. The clinical features are the same as those found in females, but owing to the smaller amount of tissue, involvement of skin and nipple is frequent as well as adherence to pectoral fascia or muscle. Metastasis to axillary glands is a frequent finding and may be the feature which brings the patient for treatment. The pathological features, including histological appearances, are similar to those of females. Radical mastectomy and deep X-ray therapy form the basis of treatment. In three of the 19 cases in the author's series the condition was inoperable when the patient first came under observation. The end-results are unfavourable. Eighteen patients survived treatment, one having died from a pulmonary embolus. Four of the 18 are alive and free from disease after twenty-nine years, three years and three months, two years and seven months, and eight months respectively. One patient is alive and receiving treatment for local recurrence near the scar. Nine patients have died as a result of the breast disease and three from intercurrent disease after twenty-two years, eighteen months and eight months respectively. One patient remains untraced. Thus only three patients survived the five-year period, but only two were free from disease. The main reasons for the poor results appear to be the sparsity of tissue, which allows early dissemination, regional and general, to take place, and the late presentation of some patients who either fail to notice or ignore a lump in the breast.

Ætiological Factors in Bronchogenic Carcinoma.

E. L. WYNDER AND E. A. GRAHAM (*Archives of Industrial Hygiene and Occupational Medicine*, September, 1951) interviewed 857 persons with proved bronchogenic carcinoma and collected data on their occupations and whether they lived in urban or rural districts. After giving a statistical analysis of their results and a discussion on their findings, the authors record the following conclusions. Several factors may be responsible for the induction of primary carcinoma of the lungs. One is undoubtedly an intrinsic factor. Its nature is unknown. Other factors of exogenous nature seem to be of similar importance. Additional data on tobacco smoking indicate that tobacco is one of these other factors of major importance. The greater the amount of tobacco smoked, the greater the risk that primary carcinoma of the lungs may develop. City dusts and fumes cannot account for the increased incidence of lung cancer. A few occupations appear with greater-than-expected frequency among the lung-cancer group, even though decisive statistical evidence is lacking. Among those of the most general importance are the occupations of metal workers, painters, and workers exposed to excessive fumes of oils, gasoline, varnish and wood dust.

Brain Hernia Through the Ear.

ABRAHAM S. EFFRON, FOSTER KENNEDY AND EDITH WLADKOWSKY (*The Journal of Nervous and Mental Disease*, October, 1951) describe a case of herniation of brain into the external auditory canal with recovery. A review of the literature revealed only four such cases; death is usual. A photomicrograph shows necrotic nerve cells from the external auditory meatus. The patient, a white girl, aged fifteen years, was admitted to hospital in a coma after a truck accident. Energetic treatment with penicillin, oxygen in a tent and blood transfusion was carried out. Recovery was slow. Psychological examinations revealed some residual loss of intellectual function.

Spinal Cord Injury in the Neck without Damage to the Vertebral Column.

A. R. TAYLOR (*The Journal of Bone and Joint Surgery*, November, 1951) describes a case of cervical traumatic paraplegia in which there was no evidence of damage to vertebræ, disks or ligaments. From this case and from experimental evidence he concludes that cases of cervical paraplegia without radiographic evidence of bone damage or displacement should be regarded as the result of injuries caused by forcible hyperextension and treated as such by immobilization in slight flexion. Immobilization is necessary because there is no means of determining whether the anterior longitudinal ligament is intact or not. Traction has no value and should not be employed. The author considers that the conception of cord injury by skeletal displacement in hyperflexion with spontaneous recoil to normal relationships is untenable and should no longer influence practical management. He emphasizes the fact that to nurse such patients in hyperextension is to cause cord ischæmia. Under normal conditions the cord has a smaller margin of safety at the cervical enlargement than anywhere else. The cord swells after contusion, sometimes sufficiently to cause obstruction to the flow of cerebro-spinal fluid as judged by Queckenstedt's test. If the primary injury is dislocation by extension, hyperextension reforms the projection and compresses the cord.

Unilateral and Bilateral Lobotomy.

ALEXANDER SIMON *et alii* (*Archives of Neurology and Psychiatry*, October, 1951) have studied 33 chronic psychiatric patients who underwent either unilateral or bilateral lobotomy. The selection was by chance. Of the 16 patients with bilateral operations, 11 obtained beneficial results, but of the 17 patients with unilateral operations beneficial results were obtained by only three. Six months after the unilateral operations 14 of the patients were subjected to second stage contralateral operation, and improvement was noticed in 11 cases. The authors conclude that the bilateral operation is necessary for beneficial results in cases of chronic schizophrenia.

Lobotomy and Social Change.

J. SANBOURNE BOCKOVEN AND ROBERT W. HYDE (*The Journal of Nervous and Mental Disease*, August, 1951) discuss the application of a sociometric technique to the study of patients who have undergone lobotomy. He states that an observer unobtrusively enters a room and records in sequence the activities of the patient. The patient is represented on the chart as a diamond, whose facets represent "attention", "verbal", "action" and "no activity". Arrows, dotted lines and new diamonds plot his whereabouts in the room and the activity he displays. Such "sociograms" made before and after lobotomy lead to the conclusion that as a rule after operation patients enter into conversation more freely and are more cooperative in games. On the other hand they read less and listen less to the radio. On the whole they show a more friendly attitude to other patients.

Sternal Osteomyelitis.

DOUGLAS VELLACOTT (*The Lancet*, April 12, 1952) states that primary osteomyelitis of the sternum is rare. He reports the case of a cook, aged twenty-six years, who was admitted to hospital with a history of three weeks' pain and tightness in the chest. Nine months previously the patient had bruised an area over his *manubrium sterni* against a kitchen table. He had a hot, painful and acutely tender swelling over the sternum. He was given penicillin by the intramuscular route and operation was performed, the œdematous periosteum being incised and the anterior cortex of the bone being removed by light gouging. The wound of the skin was closed, but a small rubber tube was inserted through a stab wound for the local administration of penicillin. The wound healed by first intention. *Staphylococcus aureus* was grown from the pus.

Special Articles for the Clinician.

(CONTRIBUTED BY REQUEST.)

XX.

THE TREATMENT OF HYPERTENSION.

A BLOOD pressure reading which is constantly above 150 millimetres of mercury (systolic) and 95 millimetres (diastolic) is regarded as abnormal, but rarely does a patient require treatment for hypertension unless either complicating vascular degeneration is present or the blood pressure is regularly raised to 180 millimetres of mercury (systolic) and 110 (diastolic). In determining hypertension, it is necessary to be sure that the armlet is properly applied, as many incorrect readings are obtained by not making sure the patient's arm is relaxed, that the rubber cuff is applied over the inner side of the arm, and that in obese individuals, the length of the compressing bandage is sufficient to prevent the inflated rubber bag from protruding outside the area of pressure. If these precautions are not taken the error may be as high as 50 to 90 millimetres of mercury.

Hypertension has become increasingly common, and it is reported that 100,000 persons die each year in the United States of America from heart failure due to hypertension and a further 75,000 from cerebral accident. In one series of 30,000 autopsies with 3600 cardio-vascular deaths, 55% of the latter were primarily due to hypertension.

Hypertension has been divided into (*a*) primary and (*b*) secondary, of which the former is by far the commoner; but before the diagnosis of primary hypertension is accepted, it is necessary to rule out those conditions which produce secondary hypertension, and this differentiation has further importance, as some of the causes have a specific treatment. An adequate clinical examination, with palpation of the femoral arteries to detect feeble pulsation and lowered pressure in the legs, and palpation of the back with the patient leaning forward in order to feel for anastomotic vessels, will usually exclude coarctation of the aorta. In doubtful cases, blood pressure estimations in the legs and radiological examination of the chest will prove or disprove the diagnosis. Clinical examination and microscopic examination of the urine, together with palpation of the loins, will usually exclude polycystic kidneys, nephritis, and chronic urinary infection, which may cause hypertension.

In young people with unexplained hypertension an excretion pyelogram should be performed as unilateral renal disease may be a cause of high blood pressure. However, only in 8% of such individuals is the blood pressure greatly reduced by nephrectomy. Improvement rarely occurs in the elderly or the middle-aged, or if the kidney is grossly destroyed. An early hydronephrosis in a young person is the type of lesion in which nephrectomy is most successful.

In the elderly, prostatic obstruction frequently produces temporary hypertension and this cause should be excluded. The hypertension of Cushing's disease and other endocrine disorders may be excluded by general clinical examination.

Phæochromocytomata are very rare tumours, of which I have never recognized an example. They produce hypertension which is at first paroxysmal but later permanent, together with signs of excess adrenaline activity resembling some of the features of thyrotoxicosis. The patients sweat profusely, become irritable and nervous, and complain of severe headache during the paroxysms of hypertension. In doubtful cases the use of adrenolytic drugs, such as benzodioxane or the histamine pressor test, may clinch the diagnosis.

Primary hypertension may be either benign or malignant, the diagnosis of the latter depending on a very high diastolic pressure, evidence of renal damage and papilloedema. Usually in young people the malignant phase is rapidly progressive from the onset, whereas in the older group renal failure may develop as a result of benign hypertension. Heredity plays a big role in the production of essential hypertension, and obesity, especially if associated in the young with emotional tachycardia and fluctuating rises in blood pressure, appears to be an associated causative factor. The main cause is unknown, and all that can be stated is that the arterioles, as a result of some direct nervous, chemical or toxic stimulus, become irritable and spastic, sclerosis develops, and frequently degenerative atheromatous changes supervene. High blood pressure is met with twice as frequently in women as in men, but the major complications, such as heart failure, are twice as frequent in men.

The rise in blood pressure, unless to a very high degree, rarely produces any symptoms. Severe headaches, which are commonly occipital, and cerebral symptoms due to hypertensive encephalopathy, result from the blood pressure *per se*. It is possible that the syncopal and vertiginous attacks, frequently observed in hypertensive patients, result from variations in pressure, but they are most common in elderly patients who have been known to have bad high blood pressure for years, and consequently, degenerative arterial changes are the most likely basis for their production. The main symptoms met with in hypertensive individuals are a result of complications. The causes of death are: cardiac failure occurring on an average of ten years after the development of hypertension, in approximately 43%; coronary disease occurring in 36%; cerebral hæmorrhage occurring in 14% and renal insufficiency in 7%.

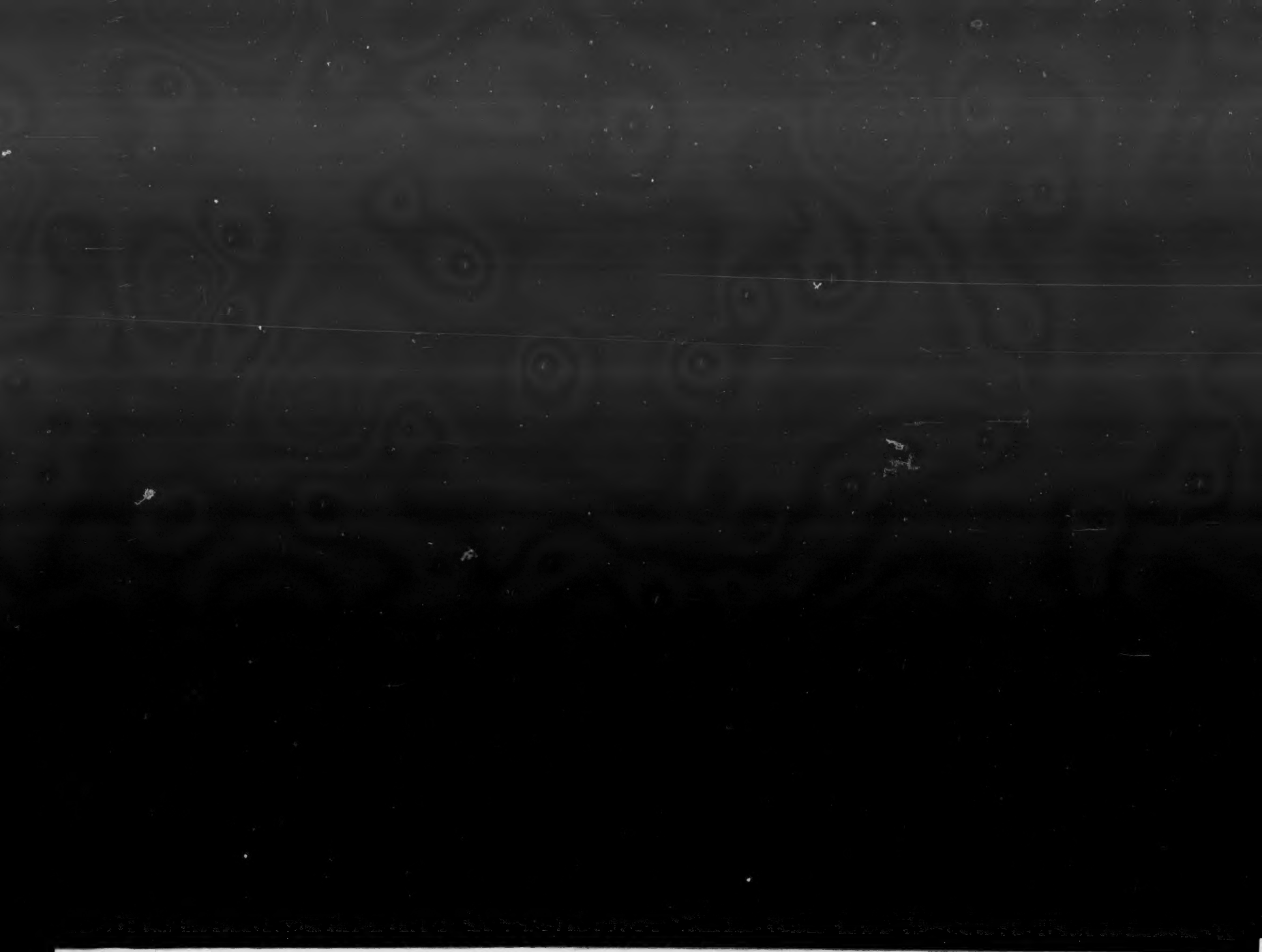
It is important to remember that although progressive hypertension in the young is very serious, the existence of high blood pressure in the elderly is compatible with a normal life expectancy. It has been stated that patients over the age of fifty-five years who, at the time that hypertension is detected, have no cardiac or renal disease can on the average expect to live within three years of their normal life span. This consideration is most important in treatment, as great harm is done by unnecessarily frightening people, because of a high manometric reading. There is no satisfactory simple treatment as yet for primary hypertension, and before embarking on a course of therapy, one must be certain that the hypertension is persistent, or that evidence of complications is present. Injudicious treatment and frequent blood pressure records can convert a person with a normal life expectancy with no symptoms and capable of fully earning his own living, into a neurotic who is frightened of work and who becomes a burden to himself and to his friends. In fact, reassurance in the non-progressive type of the disease is the most important single therapeutic agent. Combined with reassurance, a patient should be tactfully persuaded to lead his life at a more moderate rate if he is of the "high pressure business man type", but the majority of people in whom hypertension is diagnosed should be allowed to carry on with their ordinary routine. Similarly, unless they are overweight or suffering from the complications of hypertension, their diet should not be restricted. Regrettably, there are still too many doctors who advise elderly patients with non-progressive hypertension to give up meat and salt. Their diet becomes unpalatable, they eat less and not uncommonly mild vitamin deficiency defects are seen as a result of this bad advice, and the blood pressure is not influenced in any way. If the individual is overweight, a planned reduction diet should be prescribed and the patient's weight reduced. It is better to reduce the weight gradually by diets of about 1300 Calories, rather than to try sudden reductions with greatly restricted diets of about 400 to 500 Calories. Patients who take excess alcohol should be advised that this is undesirable, but no patient who is used to one or two drinks a day should be prevented from continuing this habit. Individuals who are deprived of their nightly glass of whisky become dissatisfied and do not relax as they did before. This increase in nervous tension does much more harm than the taking of a moderate amount of alcohol, which is, after all, a vascular dilating influence. Smoking in excess should be banned, as there is physiological evidence that nicotine can produce coronary constriction, but the evidence in the human being is not sufficient for doctors to ban smoking completely. Cigarettes should be restricted to five or six a day, and pipe tobacco to one ounce a week. One of the effects of this restriction is to decrease coughing and the liability to respiratory infection.

The patient should not be allowed to become constipated, but the excessive use of purgatives should be avoided. Evacuation can usually be obtained by adequate fruit, fluid and roughage in the diet. Paraffin emulsions are useful, if diet alone does not cure the costiveness. If the constipation is of a temporary nature and associated with headache, a saline purgative is of value.

Treatment of Symptoms.

Waking in the early hours of the morning and sleeplessness occur frequently in hypertensive patients suffering from degenerative cerebral arterial disease and may be very difficult symptoms to relieve. A drink of milk left by the bed and taken on waking is often helpful.

In males, a bottle to allow of urination without getting up frequently allows the individual to fall asleep when his bladder distress is relieved, whereas, if he gets up, he



becomes chilled and it is often impossible for him to return to sleep. Sometimes raising the head of the bed, or extra pillows, will help those with very high pressures, or those with commencing left-sided heart strain. The room should be well ventilated, and the clothing adequate, but not heavy. Sedatives should be avoided if possible, and no one drug should be continued for any length of time. Barbiturates are the most commonly prescribed drugs, and it is not uncommon to see patients who are regarded as suffering from cerebral vascular degeneration because of mental apathy, forgetfulness, weakness and marked ataxia, whose symptoms promptly disappear when the nocturnal barbiturate sedative is no longer taken. Patients whose difficulty is an inability to fall asleep should be given a quick-acting drug, such as "Seconal" (grains one and a half), whereas those whose difficulty is waking up early should be given one of the more slowly acting drugs such as phenobarbital or barbitone. Other sedatives that may be used to alternate with the barbituric series are potassium bromide (grains 30), syrup of chloral (two drachms) or paraldehyde two to four drachms orally or five millilitres by intramuscular injection. It should be remembered that in patients with commencing heart failure the proper use of digitalis and mercurial diuretics is more effective than sedatives.

Vertiginous attacks may be diminished in frequency by the use of a low sodium intake supplemented by potassium salts, or by the administration of small doses of sedatives, for example, phenobarbital (grain one-half) two or three times a day or antihistamine drugs such as "Anthisan" (50 milligrammes), "Benadryl" or "Phenergan". "Benadryl" is often the most effective, but is the most likely to produce toxic symptoms which in some patients are severe and consist of drawsiness, an aching feeling in the limbs, or unsteadiness.

Treatment of Complications.

Heart failure is treated in the same manner as that resulting from other causes. The failure is commonly left ventricular failure, with normal rhythm. Unless the failure is extremely acute digitalis should be administered by the slow method, rather than rapidly by massive dosage, because many elderly hypertensives are very susceptible to digitalis, and toxic symptoms, including ventricular tachycardia, are liable to occur after the administration of a relatively small amount of the drug. Two grains three times a day for the first day and then one grain three times a day are adequate, unless the failure is acute.

"Mersalyl" should be prescribed for breathlessness or frank œdema. The tendency is to use too little of this diuretic rather than too much.

Cardiac asthma is treated on the usual lines with morphine grain one-quarter). In resistant cases "Digoxin" (0·5 to 0·75 milligramme) or ouabain intravenously (grain one-quarter) may be of value, if the patient has not previously been digitalized. Aminophyllin (0·25 gramme) given intravenously is sometimes of value, but the main treatment is with adequate morphine. If the patient is extremely congested a venesection may be performed.

There is no effective treatment of cerebral hæmorrhage other than lumbar puncture if there is increasing intracranial pressure due to blood in the subarachnoid space. This may be supplemented by an intramuscular injection of 50 milligrammes of hexamethonium bromide to lower the systemic blood pressure. The same treatment is of value in hypertensive encephalopathy.

Renal failure is an end result of hypertension and little can be done for it. If it is precipitated by infection, the latter should be treated with the appropriate antibiotic. The diet should have a very low protein content and should not contain too much orange juice, which is rich in potassium, as some of the symptoms of uræmia are due to hyperkalæmia.

Treatment of High Blood Pressure.

The commonly used drugs have practically no value in reducing blood presure. Phenobarbital (grain one-half) taken three times a day or potassium bromide (grains seven and a half) is of help in the nervous type of individual. It is doubtful whether the commonly prescribed aminophyllin is of any value, except perhaps in those cases in which coronary sclerosis is present. In the nervous female with menopausal symptoms, small doses of sedative combined with synthetic follicular hormone, for example, stilbœsterol (1·0 milligramme), ethinyl œstradiol (0·01 to 0·03 milligramme), or "Conestron" (1·25 milligrammes) are of value in relieving symptoms.

Ganglionic Blocking Agents.

Recently, drugs which act by blocking the autonomic ganglia have been introduced in the treatment of hypertension. These drugs are really effective in lowering the height of the blood pressure, but they are variable in their effect, transient in their action, and, if given by mouth, irregular in their absorption. However, they give promise of a new and perhaps successful approach to the treatment of hypertension. The one most commonly used is hexamethonium bromide (C6), which is manufactured in tablets of 250 milligrammes and in ampoules of 100 milligrammes. As in some patients bromism may develop, the manufacturers are now putting on the market hexamethonium bitartrate tablets of 350 milligrammes which produce the depressor effect without the danger of bromide poisoning.

In my experience, oral administration is rarely effective, although occasionally one gets successful results. The dose has to be gradually increased until the blood pressure falls to the desired level. The usual effective dose varies from six to fourteen tablets a day, divided into three doses a day. The tablets should be crushed and given an hour before meals. The blood pressure should be taken with the patient in the standing position because the main fall, as after sympathectomy, is in this position. If this precaution is not observed, a blood pressure which is only slightly lowered by a certain dosage while the patient is lying down may fall to alarming levels when the patient assumes the upright position. It is wise, during the period of stabilization, to take the pressure reading one and two hours after the taking of the drug, whose duration of action is about three hours, although in successful cases the pressure may not rise to its preadministration level. Many patients do not get any fall of the pressure with oral administration of the drug. The majority have their pressure lowered temporarily, but quickly acquire a tolerance, and after a month or two, despite increasing doses of the drug, the pressure rises to its former level. Despite the fact that in the majority the pressure regains its old level, symptoms such as headaches are frequently relieved and the patients stoutly maintain that they are improved. An exception is individuals with nitrogen retention, in whom small doses may maintain a low pressure level. If the pressure can be maintained at a lower level relief is always given to those patients with left-sided heart failure, and retinal exudates and papilloedema slowly clear. With the large doses used orally, signs of drug overaction are common and consist of dryness of the mouth, blurring of vision due to interference with accommodation, difficulty in passing urine, and constipation, and in a few instances paralytic ileus may develop.

Smirk, of Dunedin, has advocated subcutaneous injections of the drug three times a day under properly controlled supervision. His results are most convincing and my own experience accords with his. The initial dose is 15·0 milligrammes and the blood pressure is taken by a competent technician each half-hour for two hours. If an adequate fall does not occur, the dose is increased until the pressure is reduced to the desired level, which varies with the previous height of the blood pressure, but the aim should be to reduce the systolic and diastolic pressures to about 150 and 100 millimetres of mercury. The difference between a non-effective and an effective dose is very small and may not exceed 5·0 to 10·0 milligrammes. Tolerance to the drug develops, as in the oral method, but with the smaller doses used there is scope for increasing the dose and keeping below any possible toxic level. A patient whose fall was satisfactory after an injection of 15·0 milligrammes may subsequently require a dose of 50 to 100 milligrammes three times a day. A few patients require up to 200 milligrammes per dose. During the stabilizing period, if the blood pressure is lowered too far, fainting may occur, but this can be relieved by making the patient lie down. With the use of carefully graduated doses it is practically never necessary to require intravenous injections of nor-adrenaline to raise the blood pressure, but if large doses are used without control, serious complications may ensue. I have never seen cerebral accidents develop from excessive lowering of blood pressure, but such complications have been reported. Subcutaneous injection of the drug requires a carefully organized unit to control its use, but once the patient's condition is stabilized it is fairly easy to increase the drug as required. Smirk allows intelligent patients to increase it themselves by 5·0 milligrammes, if after standing upright before a clock for one minute they do not become giddy.

Patients naturally do not relish thrice daily, self-inflicted injections, and consequently the only patients who should be placed on this routine are those patients with diastolic pressures over 130 millimetres of mercury, those with cardiac or commencing renal failure, or those with retinal

changes impairing vision. Another difficulty in treatment arises from the fact that the manufacturers do not put up the solution in a suitable 20 millilitre bottle of a 10% solution with a rubber cap, but only in 100 milligramme phials which are wasteful and difficult for the patients to use. I am convinced that this form of treatment is the most successful that has been designed for lowering the blood pressure and that the development of a longer acting, or perhaps a more easily assimilated, drug will eventually simplify treatment.

In patients with severe headache in whom oral administration of hexamethonium is ineffective and in whom subcutaneous injections are not desirable or practicable, sodium thiosulphate in doses of one and a half to five grains dissolved in syrup or prescribed in capsules three times a day may produce relief. The administration of this drug should be controlled by blood estimation and a level of 6·0 to 10·0 milligrammes per 100 millilitres should be maintained.

The *veratrum viride* alkaloids taken by mouth have been used in the treatment of hypertension, but only one patient in five can take the drug because of vomiting, and they are too dangerous for general use.

Sympathectomy.

Sympathectomy should be restricted to the group of patients for whom subcutaneous administration of hexamethonium was advocated, namely, young people with a progressively rising pressure, those with severe symptoms and those with malignant hypertension without established renal failure. The operation, even with careful selection of patients, has not been extremely satisfactory, as frequently the blood pressure rises after the operation. Occasionally dramatic results occur. Should the pressure rise after sympathectomy, small oral doses of hexamethonium are sometimes effective in reducing the level.

In my opinion sympathectomy has a limited use in treatment, but should be used for the types of cases described above if orally administered hexamethonium is ineffective and there are not facilities for controlling the subcutaneous injection of hexamethonium, or if the patient is opposed to injections.

Diets with a Low Sodium Content.

The Kempner diet of rice and fruit, and diets with a sodium content below 250 milligrammes, are often effective in relieving severe symptoms and lowering tension, but they are very unpleasant and few patients will continue with them for any length of time. They are suitable for the treatment of acute emergencies rather than for the permanent treatment of chronic hypertension. Their use often increases the action of hexamethonium.

J. G. HAYDEN,
Melbourne.

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

GOULBURN HOSPITAL.[1]

Colonial Secretary's Office,
Sydney, January 3, 1834.

James Bowman, Esq.

Sir,

I am directed by His Excellency the Governor to inform you that Mr Patrick HARNETT is appointed Assistant Colonial Surgeon from the 1st instant to be stationed at GOULBURN PLAINS where a Hospital is now building under the direction of the permanent Board and will shortly be fit for the reception of patients. It is intended that the assigned servants of Settlers and Convicts in Government employ requiring Hospital treatment from any place to the Southward of BONG BONG should be received into the Goulburn Hospital instead of being sent to Liverpool as is now the case. It is intended also that Mr Harnett should visit all the Iron Gangs and Road Parties in the Southern District for which he will be allowed forage for a horse. A quarter for the Surgeon is now in course of erection adjoining to the Hospital and no allowance for Lodging Money is to be made in this case. But Mr Harnett is to proceed to Goulburn to expedite the completion of the Hospital and to perform the duty of visiting Gangs and will receive his Pay and Forage Allowance from the 1st January instant.

Mr Harnett has been apprised of his appointment and desires to wait upon you for instructions.

I have, &c.,
ALEXR. MCLEAY.

Colonial Secretary's Office,
Sydney, May 9, 1834.

The Inspector of Colonial Hospitals.

Sir,

I have had the honour to receive and submit to the Governor your letters of 28 February and 2nd April the former enclosing one from MR HARNETT representing the necessity of additions to the Hospital at Goulburn, and the latter transmitting from the same Gentleman an application for lodging allowance. In reply I am directed to inform you that a Dispensary at the end of the Main Building has been contracted for, but that the question of any additions cannot be entertained until the work already undertaken is completed. With regard to Mr Harnetts quarters, I am directed by His Excellency to request you will point out to that gentleman, that on soliciting to be appointed and sent to Goulburn, he was expressly informed that his quarters would not be ready for some time and that he was not to receive any allowance in lieu. Had this arrangement been then objected to by him, his appointment would not have taken place until the Quarters were finished. For the same reasons he ought not in his letter to you dated 22nd February to speak of an awkward position which he thus took up at his own desire and against advice.

I have, &c.,
T. C. HARRINGTON.

[1] From the original in the Mitchell Library, Sydney.

Correspondence.

GLYCOGEN STORAGE DISEASE.

SIR: Glycogen storage disease (von Gierke's or van Creveld's disease) is a rare and fatal disorder. Two years ago, at the Banting Institute, Toronto, I carried out some experiments which looked promising from the therapeutic angle, but was prevented by illness from continuing them at that time. Owing to the scarcity of cases, I would be most grateful if any physician having a patient suffering from this disease, or knowing of such a case, would be kind enough to communicate with me.

Yours, etc.,

Department of Physiology, University of Sydney,
April 2, 1952.
DAVID MONK ADAMS.

CASE OF CARBON MONOXIDE POISONING TREATED BY REPLACEMENT BLOOD TRANSFUSION.

SIR: We read with interest the report of a case of carbon monoxide poisoning treated by replacement blood transfusion (THE MEDICAL JOURNAL OF AUSTRALIA, March 8, 1952, page 331).

Certain points come to mind. Firstly a conclusion is drawn that "it is indicated only for such patients as do not respond to the usual methods of treatment". It would seem that in this case the usual methods of treatment did not include the time-honoured injection of methylene blue; but a more pertinent objection to this statement is that with blood as valuable as it is these days it would be far better to use this treatment as an immediate measure before any anoxic cerebral damage occurs. Secondly, the method of doing the replacement transfusion need not involve incision of the radial artery had a length of polythene tubing been inserted through the saphenous vein in the groin into the inferior *vena cava*.

We have recently performed a five pints replacement transfusion on a forty-year-old gas worker who suffered considerable exposure to carbon monoxide while repairing gas pipes underground. The procedure was successful, and the patient made a good recovery. Therefore, this method of treatment could be used as an immediate measure in all severe cases of carbon monoxide poisoning.

Yours, etc.,
H. D. BREIDAHL.
I. H. CUMING.

Alfred Hospital,
Prahran, S.1,
Victoria.
March 27, 1952.

THE VALUE OF GOAT'S MILK.

SIR: Recently adverse publicity was given in the Sydney daily Press to goat's milk in an article written under the *nom de plume* of "Medico". The letter implied that brucellosis in goats was endemic throughout Australia and that considerable danger existed to persons consuming goat's milk or eating insufficiently cooked goat's flesh.

A few years ago a prominent veterinarian spent three years exclusively on brucellosis studies; during this time blood samples from goats from all over Australia were examined by agglutination tests for *Brucella melitensis*. It is interesting to note that not one case of *B. melitensis* infection was detected. On the other hand *B. abortus* infection in cattle was found in up to 90% of cows in herds supplying raw milk.

The value of goat's milk in protein allergy cases, infantile eczemas, duodenal abnormalities and other conditions of impaired digestive ability is well known and its use should be fostered rather than condemned by persons not qualified to do so. This letter is written in the hope that medical practitioners may know that goat's milk may be recommended without prejudice and with the knowledge that this product is a specific therapeutic agent in such selected cases.

Yours, etc.,
N. B. KING, B.V.Sc.,
Honorary Veterinary Surgeon,
Goat Society of Australia.

27A Ogilvy Street,
Peakhurst,
New South Wales.
April 4, 1952.

The Royal Australasian College of Physicians.

EXAMINATION FOR MEMBERSHIP.

AN examination for Membership of The Royal Australasian College of Physicians will take place in September-October, 1952. The written examination will be held on Saturday, September 6, in capital cities of the Commonwealth where candidates are offering. The clinical examination will take place in Sydney from Tuesday to Thursday, October 14 to 16, 1952.

Only those candidates whose answers in the written examination have attained a satisfactory standard will be asked by the Censor-in-Chief to proceed to the clinical examination.

Applications to appear before the Board of Censors should be made in the prescribed form and must be in the hands of the Honorary Secretary of the College not later than Saturday, August 9, 1952. Application forms are obtainable from the Honorary Secretary, 145 Macquarie Street, Sydney.

WUNDERLY TRAVELLING SCHOLARSHIP.

THE Royal Australasian College of Physicians proposes to award the Wunderly Travelling Scholarship for 1953 for the post-graduate education and training abroad of young physicians in the diagnosis and management of thoracic disease. The value of each scholarship is one thousand pounds Australian currency. The scholarship will be tenable by graduates in medicine of a university approved by the College, who hold a Doctorate of Medicine and/or a Fellowship or Membership of The Royal Australasian College of Physicians or of the Royal College of Physicians of London, but the holding of a higher degree or diploma is not an absolute condition of the award.

Information relating to the scholarships may be obtained upon application to the Honorary Secretary of the College at 145 Macquarie Street, Sydney.

Post-Graduate Work.

THE MELBOURNE PERMANENT POST-GRADUATE COMMITTEE.

PROGRAMME FOR JUNE, 1952.

THE Melbourne Permanent Post-Graduate Committee announces the following programme for June, 1952.

Classes for Higher Degrees and Diplomas, Part II.

Cardiology.

Lectures in cardiology, under the direction of Dr. L. E. Rothstadt, will be given on Tuesday and Friday afternoons at 2 o'clock, as follows: June 3, "Diseases of the Auriculo-Ventricular Valves", Dr. Maurice V. Clarke (Saint Vincent's Hospital); June 6, "Treatment of Congestive Heart Failure", Dr. J. T. Cahill (Saint Vincent's Hospital); June 10, "Aortic Valve Disease", Dr. K. J. Grice (Royal Melbourne Hospital); June 13, "Aspects of Arteriosclerotic Heart Disease", Dr. L. E. Rothstadt (Royal Melbourne Hospital); June 17, "Constrictive Pericarditis, Diagnosis and Treatment with Cases Illustrating", Dr. Morris Davis (Alfred Hospital); June 20, "Congenital Heart Disease", Dr. H. B. Kay (Alfred Hospital).

The fee for the foregoing course is £3 3s., or 10s. 6d. per demonstration.

Course in Gastro-Intestinal Disorders.

A course in gastro-intestinal disorders, under the direction of Dr. R. R. Andrew, will be held on Tuesday and Friday afternoons at 12 o'clock, as follows: June 24, "Chronic Diarrhœa", Dr. R. R. Andrew (Alfred Hospital); June 27, "Peptic Ulcer", Dr. P. J. Parsons (Alfred Hospital); July 1, "Gastritis", Dr. Ian Wood (Royal Melbourne Hospital—Ward 3E); July 4, "Some Aspects of Steatorrhœa", Dr. Howard Williams (Children's Hospital); July 8, "Some Aspects of Liver Disease", Dr. W. E. King (Royal Melbourne Hospital).

The fee for the foregoing course is £2 12s. 6d., or 10s. 6d. per demonstration.

Flinders Naval Depot.

A demonstration on "The Management of Dyspepsia" will be conducted by Mr. J. Grayton Brown at 2.30 p.m. on Wednesday, June 11, at Flinders Naval Depot, by arrangement with the Royal Australian Navy.

Courses for Higher Degrees and Diplomas, Part I.

The courses for higher degrees and diplomas, Part I, will be continued at university departments.

D.D.R. PART II.

It has been decided to hold a course for Part II of the D.D.R., commencing about the middle of July, 1952. This course will involve a series of lectures and demonstrations in radio-diagnosis, and also a short course in special pathology.

ENROLMENTS.

Enrolments for metropolitan courses should be made with the Melbourne Permanent Post-Graduate Committee, 394 Albert Street, East Melbourne (telephone, JM 1547).

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Week-End Course at Broken Hill.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that, in conjunction with the Broken Hill Medical Association, a week-end course will be held at the Broken Hill and District Hospital on Saturday and Sunday, May 31 and June 1, 1952. The programme is as follows:

XUM

Saturday, May 31.—10.30 a.m., "Management of Heart Failure", Dr. Frank Ritchie; 11.30 a.m., "Uterine Bleeding", Dr. George Stening; 2 p.m., "Surgical Problems in General Practice", Dr. V. M. Coppleson; 3 to 5 p.m., seminar, "Recent Therapeutic and Other Advances", Dr. V. M. Coppleson, Dr. George Stening and Dr. Frank Ritchie.

Sunday, June 1.—10 a.m., seminar on a subject to be chosen, Dr. V. M. Coppleson, Dr. George Stening and Dr. Frank Ritchie; 11 a.m., question time and general discussion; 2.30 p.m., film.

The fee for attendance will be £5 5s. Those wishing to attend are requested to communicate with Dr. F. Schlink, Honorary Secretary, Broken Hill Medical Association, 252 Mica Street, Broken Hill, as soon as possible.

Australian Medical Board Proceedings.

NEW SOUTH WALES.

THE following have been registered, pursuant to the provisions of the *Medical Practitioners Act*, 1938-1950, as duly qualified medical practitioners: Blunt, Arthur Leslie, M.R.C.S. (England), L.R.C.P. (London), 1915; Dooley, Richard Maurice, M.B., B.Ch., 1945 (Univ. Dublin); Downing, John, M.B., B.Ch., 1926 (Nat. Univ. Ireland); Fenwick, Clennell Cooke, M.B., B.S., 1923 (Univ. Durham); Fish, Mervyn Thomas, M.B., B.S., 1950 (Univ. Melbourne); Frazer, Atholl Lovat, M.R.C.S. (England), L.R.C.P. (London), 1938, A.D.M.R. (London), 1949; Mitchell, Paul Wanostrocht, M.B., B.S., 1948 (Univ. Queensland), D.T.M. and H. (Sydney), 1950; Randell, William Richard, M.B., B.S., 1947 (Univ. Adelaide); Robinson, Rosslyn Byers, M.B., B.S., 1950 (Univ. Melbourne).

The following additional qualifications have been registered: O'Connell, Brian Patrick (M.B., B.S., 1945, Univ. Sydney), M.R.C.P. (London), 1950; Thwaite, Thomas John (M.B., B.S., 1944, Univ. Sydney), M.S., 1952 (Univ. Sydney).

TASMANIA.

THE following have been registered, pursuant to the provisions of the *Medical Act*, 1918, as duly qualified medical practitioners: Cribb, George Desmond, L.R.C.P., M.R.C.S. (England), 1939, F.R.C.S. (England), 1950; Hope, Bertram Kendall, M.B., B.S., 1951 (Univ. Sydney); Eadie, Clive Menzies, M.B., B.S., 1912 (Univ. Melbourne).

Obituary.

HAROLD VERNON FOXTON.

HAROLD VERNON FOXTON was born at Stanthorpe, Queensland, in 1878, and lived there during early childhood. His father, Colonel J. F. G. Foxton, moved to Brisbane about 1885, and the son was educated at the Bowen House School and at the Brisbane Grammar School. On leaving school he entered his father's office and studied law for a short time, coming first in the State in his preliminary examination. He then commenced his medical course at the University of Melbourne and graduated in the early years of the present century.

After graduation Harold Vernon Foxton returned to Queensland to the staff of the Brisbane Hospital for three years and then entered the mental hospital service, becoming a resident medical officer at Goodna Mental Hospital with the right of outside practice. He remained in the service for some years, becoming medical superintendent at the Sandy Gallop Asylum.

His first wife, Mary Foxton, died in 1914. Their son, Dr. J. R. V. Foxton, is now Director of Mental Hygiene in Tasmania.

At the outbreak of World War I he enlisted and saw service on Gallipoli and in France, and for a time was senior medical officer on troopships in the Mediterranean area.

On his return from France Foxton accepted a position on the staff of the Victorian Eye and Ear Hospital and eventually became medical superintendent.

He then returned to Queensland and followed this branch of medicine until his retirement in September, 1951. During these years he served the Brisbane Hospital as an honorary aural surgeon and later joined the staff of the Mater Misericordiæ Hospital, where he became head of his department. He also worked for the Repatriation Department from the time of his return to Queensland until his retirement. He was a foundation Fellow of the Royal Australasian College of Surgeons.

Harold Foxton was for many years a member of the Queensland Council of the British Medical Association and was twice elected State President.

His main sport and hobby since early boyhood was sailing. He was a member of the Royal Queensland Yacht Club and owned three well-known yachts, all named *Irex*, and was a keen entrant in many races in these yachts.

His death occurred after a long illness on February 14, 1952, at his home. He is survived by his second wife and two children, a daughter and son, the son being in his final year of medicine at the University of Queensland.

Dr. Basil Hart writes: I have known Harold Foxton nearly all my life. His family and mine have always been friends and we formed a friendship in our boyhood days that lasted all through the years. When the first war broke out Foxton was the medical superintendent of the Mental Hospital at Ipswich. He obtained leave of absence and joined the Australian Imperial Force and left with the First Australian General Hospital in the *Kyarra* in 1914. He served in Egypt, Gallipoli and France, returning in 1919.

After the war he specialized at the Victorian Eye and Ear Hospital (Melbourne), and was for a time superintendent of that hospital. He returned to Brisbane and practised as an ear, nose and throat surgeon in that city until his death.

He was on the honorary staff of the Brisbane General Hospital for a time, but resigned that position owing to pressure of work. He was also on the honorary medical staff of the Mater Misericordiæ Hospital, but resigned that position when there was some trouble between the staff and the management. He was also on the staff of the Repatriation Department at Rosemount and Greenslopes Hospitals. This position was resigned just a few months before his death.

Foxton was a quiet man of strong character and firm convictions. He was intensely interested in his work, and in addition to being very adequate and efficient had naturally a kindly and courteous manner that inspired with affection, confidence and respect all those with whom he came in contact. He was especially keen on his repatriation work and always had a soft spot in the corner of his heart for the "returned soldier".

He was President of the Queensland Branch of the British Medical Association in 1927. He was always most punctilious in all his dealings with other members of the profession, and it was always a pleasure to send a case to him. He was a Fellow of the Royal Australasian College of Surgeons. He was a man who delighted in his home, his garden and his family life. A great interest was sailing, and he spent most of his spare time in his boat on Moreton Bay, where he was well known to all the boating fraternity.

The last few years he suffered greatly from the condition which eventually caused his death, but in spite of repeated attacks he persevered with his work until he resigned a few months ago. The last two months he suffered considerably, but faced all his troubles with a calm courage. He was so far fortunate in that he had in his house a devoted and experienced nurse in the person of his wife and was thus able to avoid a prolonged stay in hospital, which he would have disliked exceedingly. His stay in hospital was always as short as he could persuade his medical advisers to allow.

He was married twice. His first wife was Miss Mary Cater, who died in 1914, leaving one son, Dick, who is in the State medical service in Tasmania. After the war he married Miss Anne Bell, of Murrnong Station, New South Wales, who had herself served in the nursing service of the Australian Imperial Force all through the war in Egypt and in France. Besides his widow he leaves a married daughter, Mrs. Kelly, who before her marriage was a trained nurse, and another son, Alec, who is in his final year of medicine in the University of Queensland.

JAMES SPITTAL BUCHANAN.

WE regret to announce the death of Dr. James Spittal Buchanan, which occurred on April 26, 1952, at Toorak, Victoria.

BENJAMIN CROWNSON JOEL.

WE regret to announce the death of Dr. Benjamin Crownson Joel, which occurred on April 30, 1952, at Elwood, Victoria.

JOHN HILLMAN HORNBROOK.

WE regret to announce the death of Dr. John Hillman Hornbrook, which occurred on May 5, 1952, at Bellevue Hill, New South Wales.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Jacks, Laurence Maurice, M.B., B.S., 1950 (Univ. Sydney), 129 New South Head Road, Vaucluse.

Larbalestier, Peter Senis, M.B., B.S., 1945 (Univ. Sydney), D.D.R., 1950 (Univ. Sydney), 69 Hunter Street, Newcastle.

The undermentioned have been elected members of the New South Wales Branch of the British Medical Association: Barbour, Edmund, M.B., B.S., 1951 (Univ. Sydney); Bradbury, Roger, provisional registration, M.B., 1952 (Univ. Sydney); Breyer, Bruno Zdenko, registered in accordance with *Medical Practitioners Act*, 1938-1950, Section 17 (2); Collier, Beryl, provisional registration M.B., 1952 (Univ. Sydney); Collison, Jeanne Margaret, provisional registration M.B., 1952 (Univ. Sydney); Davis, Joseph Ivan, provisional registration M.B., 1952 (Univ. Sydney); Degotardi, Colin Boyne, M.B., B.S., 1951 (Univ. Sydney); Doust, Kenneth McGowen, provisional registration M.B., 1952 (Univ. Sydney); Duke, John Swinnerton, provisional registration M.B., 1952 (Univ. Sydney); Fisher, June Ida Wyndham, provisional registration M.B., 1952 (Univ. Sydney); Goard, Kenneth Edwin, provisional registration M.B., 1952 (Univ. Sydney); Haddan, Frank Ellison, provisional registration M.B., 1952 (Univ. Sydney); Harbison, Douglas John, provisional registration M.B., 1952 (Univ. Sydney); Hardwicke, Noelene Joan, provisional registration M.B., 1952 (Univ. Sydney); Harris, Henry Thomas Wilfred, M.B., 1951 (Univ. Sydney); Hibbard, Loraine Clare, provisional registration M.B., 1952 (Univ. Sydney); Joneshart, Cycil Luke, provisional registration M.B., 1952 (Univ. Sydney); Kendall, Peter Paul, provisional registration M.B., 1952 (Univ. Sydney); Kent, Peter William, provisional registration M.B., 1952 (Univ. Sydney); Klajncwajg, Zygmunt, registered in accordance with the provisions of Section 17 (1) (*c*) of *Medical Practitioners Act*, 1938-1950; Kosman, Edward, M.B., B.S., 1951 (Univ. Sydney); Lopes, Anthony Giuseppe, provisional registration M.B., 1952 (Univ. Sydney); Lorence, George Stephen, provisional registration M.B., 1952 (Univ. Sydney); Maxwell, Ian, provisional registration M.B., 1952 (Univ. Sydney); McDonald, Alma Monica Dorothea, M.B., 1929 (Univ. Sydney); McIntyre, John Donald, provisional registration M.B., 1952 (Univ. Sydney); McKerihan, Robert Henry Kenrick, provisional registration M.B., 1952 (Univ. Sydney); Nelson, John Ross, provisional registration M.B., 1952 (Univ. Sydney); Reiner, Zenon, registered in accordance with the provisions of Section 17 (1) (*c*) of *Medical Practitioners Act*, 1938-1950; Rushworth, Robin Geoffrey, provisional registration M.B., 1952 (Univ. Sydney); Saunders, Colin Bateson, provisional registration M.B., 1952 (Univ. Sydney); Segelov, John Nathan, provisional registration M.B., 1952 (Univ. Sydney); Sinclair, Russell Wade, provisional registration M.B., 1952 (Univ. Sydney); Steele, George Warwick, provisional registration M.B., 1952 (Univ. Sydney); Stitz, Alan James, provisional registration M.B., 1952 (Univ. Sydney); Tugwell, Kingsley Frederic, provisional registration M.B., 1952 (Univ. Sydney); Tymms, Brian Blake, provisional registration M.B., 1952 (Univ. Sydney); Upton, Ralph Denison, provisional registration M.B., 1952 (Univ. Sydney); Walters, Peter, provisional registration M.B., 1952 (Univ. Sydney); Weisz, Andrew, registered in accordance with the provisions of Section 17 (1) (*c*) of *Medical Practitioners Act*, 1938-1950; Wells, Ernest

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED APRIL 19, 1952.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	..	..	..	..	..	..	..	..	..
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	..	..	..	..	..	..	..
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	..	..	15(12)	..	..	..	2	..	17
Diphtheria	3(1)	9(7)	7(4)	..	4(4)	..	..	..	23
Dysentery (Bacillary)	..	2(2)	7(6)	2(2)	..	..	..	..	11
Encephalitis	..	1	..	..	..	..	..	..	1
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	..	..	..	..	4(1)	..	..	..	4
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	..	..	..	..	..	..	..
Malaria	..	..	..	..	..	..	..	..	..
Meningococcal Infection	5(3)	5(1)	..	1	1(1)	..	..	..	12
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	8(2)	7(3)	2(2)	19(14)	2(2)	..	..	..	38
Puerperal Fever	..	..	..	..	..	..	..	..	..
Rubella	..	24(23)	..	..	..	..	..	1	25
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	21(9)	47(23)	2	4(2)	1(1)	..	..	..	75
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	1	3(1)	..	..	..	..	..	4
Trachoma	..	..	..	..	..	..	..	..	..
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	23(13)	7(4)	23(19)	8(6)	8(6)	3(1)	..	..	72
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	2	..	..	..	..	..	2
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

Kenneth Bethune, L.R.C.P. (Edinburgh), L.R.C.S. (Edinburgh), L.R.F.P.S. (Glasgow), 1951; Nowell, Thomas Algernon, M.B., Ch.B., 1944 (Victoria University, Manchester).

The undermentioned have applied for election as members of the South Australian Branch of the British Medical Association:

Morey, Harry Francis, M.B., B.S., 1947 (Univ. Sydney), Western Clinic, 150 Henley Beach Road, Torrensville.

Moncrieff, Rostrevor Brooke, M.B., B.S., 1951 (Univ. Adelaide), 22 St. Andrew's Street, Walkerville.

Morgan, Owen Brakspear, M.B., B.S., 1951 (Univ. Adelaide), 76 Cheltenham Street, Malvern.

Bell, Franklyn Gilbert, M.B., B.S., 1949 (Univ. Adelaide), Royal Adelaide Hospital, North Terrace, Adelaide.

The undermentioned have been elected members of the South Australian Branch of the British Medical Association: Hoare, Lehonde Lucas, M.B., B.S., 1949 (Univ. Adelaide); Gold, Ronald Geoffrey, M.B., B.S., 1951 (Univ. Adelaide); Jessup, Allan Aubrey, M.B., B.S., 1951 (Univ. Adelaide); Wells, Barbara Condon, M.B., B.S., 1951 (Univ. Adelaide); Solly (*née* Begg), Janet Elizabeth, M.B., B.S., 1951 (Univ. Adelaide); Lander, Harry, M.B., B.S., 1951 (Univ. Adelaide); Hasenohr, Geoffrey, M.B., B.S., 1948 (Univ. Adelaide); Manthorpe, Thomas Dion, M.B., B.S., 1950 (Univ. Adelaide); Morgan, Lloyd Kenneth, M.B., B.S., 1951 (Univ. Adelaide); Duguid, William George, M.B., B.S., 1948 (Univ. Adelaide); Beare, Thomas Hudson, M.B., B.S., 1951 (Univ. Adelaide); Flaherty, James Aloysius, M.B., B.S., 1951 (Univ. Adelaide); Perret, Lance Victor, M.B., B.S., 1951 (Univ. Adelaide).

Medical Practice.

POLICE OFFENCES (AMENDMENT) ACT, 1908 (NEW SOUTH WALES).

THE following proclamation has been made in the *Government Gazette of the State of New South Wales* of April 24, 1952, relative to the *Police Offences (Amendment) Act*, 1908.

I, SIR JOHN NORTHCOTT, Knight Commander of the Most Distinguished Order of Saint Michael and Saint George, Companion of the Most Honourable Order of the Bath, Member of the Royal Victorian Order, Lieutenant-General on the Retired List of the Australian Military Forces, Governor of the State of New South Wales and its Dependencies in the Commonwealth of Australia, with the advice of the Executive Council, do, by this my Proclamation, declare that Part VI of the Police Offences (Amendment) Act, 1908, as amended, shall apply to

> Dromoran (also known as Methorphinan) (3-hydroxy-N-methyl Morphinan), its salts and any preparation, admixture, extract or other substance containing not less than one-fifth per centum of Dromoran

in the same manner as it applies to the drugs mentioned in paragraph (a) of subsection (2) of Section 18 of the said Act.

Signed and sealed at Sydney this ninth day of April one thousand nine hundred and fifty-two.

By His Excellency's Command.

(Sgd.) CLIVE EVATT.

GOD SAVE THE QUEEN!

Medical Appointments.

Dr. H. B. Taylor and Dr. C. B. Cox have been appointed analysts for the purposes of the *Pure Food Act*, 1908, New South Wales.

Dr. B. H. Peterson has been appointed to the Division of Mental Hygiene in the Department of Public Health, New South Wales.

Dr. Annis Macalister Henderson has been appointed to the Baby Health Centres, Department of Public Health, New South Wales.

Dr. W. M. Moore has been appointed honorary medical officer at the Mount Gambier Hospital, South Australia.

Notice.

THE Women's Hospital (Crown Street, Sydney) Clinical Society will hold a clinical evening in the nurses' lecture hall at 8.15 p.m. on Thursday, May 22, 1952, at which the following films will be shown: "Complete Exenteration of Pelvis", "Hypertension due to Pheochromocytoma". These films have just been obtained from America and should make a very interesting evening. Some short travel films in colour will be shown by Dr. F. Bellingham.

Diary for the Month.

MAY 19.—Victorian Branch, B.M.A.: Finance Subcommittee.
MAY 20.—New South Wales Branch, B.M.A.: Medical Politics Committee.
MAY 21.—Western Australian Branch, B.M.A.: General Meeting.
MAY 22.—New South Wales Branch, B.M.A.: Clinical Meeting.
MAY 22.—Victorian Branch, B.M.A.: Executive Committee.
MAY 23.—Queensland Branch, B.M.A.: Council Meeting.
MAY 27.—New South Wales Branch, B.M.A.: Ethics Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federal Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

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MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

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